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RHÔNE-POULENC

Contains No CBI

TOXICOLOGY DEPARTMENT
P.O. BOX 12014, 2 T.W. ALEXANDER DRIVE
RESEARCH TRIANGLE PARK, NC 27709
(919) 549-2000 TELEFAX (919) 549-8525
INTERNATIONAL TELEX NUMBER 4999378–ANSWERBACK APC RTP

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October 27, 1992

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Office of Toxic Substances
US Environmental Protection Agency
401 M Street, SW
Washington, DC 20460

Attn: Section 8(e) Coordinator (CAP Agreement)

RE: Report Submitted Pursuant to the TSCA Section 8(e) Compliance Audit Program

CAP ID No.: 8ECAP - 0004

Dear Sir/Madam:

On behalf of Rhône-Poulenc Inc. (RPI, CN 5266, Princeton, NJ 08543-5266) and its subsidiary Rhône-Poulenc Ag Company (RPAC), the attached study report is being submitted to the Environmental Protection Agency (EPA) pursuant to the Toxic Substances Control Act (TSCA) Section 8(e) Compliance Audit Program and the Agreement for a TSCA Section 8(e) Compliance Audit Program (CAP Agreement) executed by RPI and EPA.

The enclosed study report provides information on M&B 46030. Its CAS number and chemical index name are 120068-37-3 and 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(trifluoromethyl)sulfinyl]-1H-pyrazole-3-carbonitrile. This chemical is manufactured in Europe and imported by RPAC for pesticide research and development.

No claims of confidentiality are made for this submission. Please note that RPAC released previous confidentiality claims for the subject chemical on September 8, 1992. The title of the enclosed report is "M&B 46030: Preliminary Toxicity Study by Dietary Administration to CD Rats for Two Weeks". The following is a summary of the adverse effects observed in this study.

This study is being submitted under Section 8(e) because of the clinical signs observed. Groups of 5 male and 5 female CD rats received test material at dietary levels of 0, 500, 750, 1000, or 1500 ppm for 2 weeks. All animals died or were sacrificed at 1000 and 1500 ppm during the first three days of treatment. At 750 ppm, 3 males and 4 females died during the study. At 500 ppm, 2 males and 1 female died during the study. Clinical signs included piloerection, spastic muscle reaction, and hunched posture.

Seven previous TSCA Section 8(e) notices were submitted on this chemical. The EPA Document Control Numbers for these submissions are 8EHQ-0191-1162S, 8EHQ-0391-1199S, 8EHQ-0591-1232S, 8EHQ-0791-1284S, 8EHQ-0791-1285S and 8EHQ-0891-1315S, and

DISCLOSURE 8-12-94

8EHQ-0392-2540S. Also several Section 8(e) notices will be submitted on this compound under the CAP.

In total, RPI is submitting three copies of the enclosed report and this cover letter: an original and two copies.

Further questions regarding this submission may be directed to the undersigned at 919-549-2222.

Sincerely,

Glenn S. Simon, PhD, DABT
Director of Toxicology

LSR Schedule No : RHA/422/46030
LSR Report No : 90/RHA422/1272

M&B 46030: PRELIMINARY TOXICITY STUDY BY DIETARY ADMINISTRATION TO CD RATS FOR TWO WEEKS

FINAL REPORT

Data requirement

Guideline No. 82-1

Study Period Completed on

11 January 1991

Study Director

P. Aughton

To:
Rhône-Poulenc Agrochimie
14-20 rue Pierre Baizet
BP 9163
69263 Lyon Cedex 09
France

From:
Life Science Research Limited
Eye
Suffolk IP23 7PX
England

Draft: 7 December 1990
Final: 31 January 1991

M&B 46030: PRELIMINARY TOXICITY STUDY BY DIETARY ADMINISTRATION TO CD RATS FOR TWO WEEKS

FINAL REPORT

LSR Schedule No : RHA/422/46030
LSR Report No : 90/RHA422/1272

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA 10(d)(1)(A), (B), or (C).

Company Rhône-Poulenc Agrochimie .....

Company Agent: ..... Date: .....

....

M&B 46030: PRELIMINARY TOXICITY STUDY BY DIETARY ADMINISTRATION TO CD RATS FOR TWO WEEKS

FINAL REPORT

LSR Schedule No : RHA/422/46030
LSR Report No : 90/RHA422/1272

I declare that the report following constitutes a true and faithful account of the procedures adopted and the results obtained in the performance of this study.

The aspects of the study conducted by Life Science Research were performed in accordance with the principles of Good Laboratory Practice Standards or Guidelines relating to non-clinical studies as follows:

Current OECD Good Laboratory Practice Principles
Current DH Principles of Good Laboratory Practice
Current EPA Pesticide Programs Good Laboratory Practice Standards
Current Japanese Good Laboratory Practice Standards on Agricultural Chemicals.

The following exceptions applied:

Owing to its preliminary nature no Quality Assurance procedures were conducted on this particular study. Inspections were however conducted and data and reports reviewed on other studies carried out in the same animal and laboratory areas during the same period as this study.

Quality control assays of the diet-test substance admixtures were not performed.

It is not considered that these exceptions from GLP influenced the validity of the data or report.

The Study Director fulfilled the responsibilities required by these regulations.

P. Aughton, B.Sc., Dip.R.C.Path., C.Biol., M.I.Biol.
(Study Director)

P Aughton
.....
Date: 31 January 1991

.....

(For Submitter)

Date:.....

.....

(For Sponsor)

Date:.....

M&B 46030: PRELIMINARY TOXICITY STUDY BY DIETARY ADMINISTRATION TO CD RATS FOR TWO WEEKS

FINAL REPORT

LSR Schedule No : RHA/422/46030
LSR Report No : 90/RHA422/1272

FLAGGING STATEMENTS

This page is reserved for flagging statements as may be required by EPA in accordance with PR Notice 86-5.

M&B 46030: PRELIMINARY TOXICITY STUDY BY DIETARY ADMINISTRATION TO CD RATS FOR TWO WEEKS

FINAL REPORT

LSR Schedule No : RHA/422/46030
LSR Report No : 90/RHA422/1272

I have reviewed this report and concur with its contents.

D.M. Virgo, B.Sc.
(Chief Toxicologist)

Date: 30 January 1991

We, the undersigned, were responsible for the conduct of the work and reporting of the results in the listed sections; we concur with the views expressed in the Discussion.

L.J. Freeman, B.Sc.
(Staff Toxicologist)
Section 5.1 to 5.6

Date: 30 January 1991

S. Sparrow, Ph.D., B.Vet.Med., M.R.C.V.S.
(Head, Department of Pathology)
Section 5.7

Date: 30 January 1991

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1. SUMMARY

1.1 Groups of five male and five female CD rats received M&B 46030 continuously via the diet at dietary concentrations of 500, 750, 1000 or 1500 ppm for a maximum of two weeks. A similarly constituted group received untreated diet and served to generate contemporaneous control data.

1.2 The following changes were noted:

1000 and 1500 ppm

All animals died or were killed *in extremis* during the first three days of the treatment period.

Piloerection, spastic muscle reaction and hunched posture were noted for the majority of animals which were killed.

All animals lost bodyweight and animals receiving 1500 ppm consumed little food before death.

Macroscopic changes included dark lungs, facial staining and distension of the stomach.

750 ppm

Three males and four females died during the treatment period.

Piloerection, hunched posture and spastic muscle reaction was noted for one male that died, and red staining around the muzzle was noted for several animals.

Food consumption, efficiency of food conversion and overall weight gain were markedly lower than those of their respective controls. Bodyweight losses were noted over the first four days of treatment.

Facial staining was noted for several animals at macroscopic examination.

500 ppm

Appearance and behaviour of the animals was unaffected by treatment.

Two males and one female died during the treatment period.

Food consumption, efficiency of food conversion and overall bodyweight gain were markedly lower than those of their respective controls. Bodyweight losses were noted over the first four days of the treatment period.

1.3 Treatment of CD rats with M&B 46030 at concentrations of 500, 750, 1000 or 1500 ppm resulted in deaths at all dietary levels.

The maximum tolerated level of M&B 46030 among CD rats is less than 500 ppm.

2. INTRODUCTION

The purpose of this study was to aid the assessment of the toxic effects of M&B 46030, a trifluoromethyl pyrazole insecticide, and to assist in the selection of dietary concentrations for a proposed oncogenicity study in CD rats.

The rat was used because of its acceptance as a predictor of neoplastic and toxic change in man and the general requirement by regulatory agencies for a rodent species. The CD strain was used because of the availability of background data relating to this strain. The dietary route was selected to accord with the potential major route of exposure in manufacture and use. The dietary concentrations of 500, 750, 1000 and 1500 ppm and the scheduled duration of treatment of two weeks were selected by the Sponsor.

Treatment commenced on 23 August 1990 and terminal necropsies were completed, following two weeks of treatment, on 6 September 1990.

3. TEST SUBSTANCE AND DOSAGE FORM

A 510 g sample of M&B 46030, Lot No. PGS963, was received from the Sponsor on 24 January 1990. The test substance, a fine white powder, was received in amber glass jars and stored at ambient temperature, protected from light.

The identity, strength, purity, composition, stability and methods of synthesis, fabrication or derivation of M&B 46030 were determined by the Sponsor. The certificate of analysis of M&B 46030 after manufacture is presented in Appendix 1.

Before use of this consignment of test material a 2 g subsample was taken and stored in a glass container alongside the major part of the sample. It was subsequently retained in the archives as raw data.

Investigations of stability, homogeneity and achieved concentration of test diet were not performed for this study. Acceptable stability and homogeneity of M&B 46030 in diet at room temperature were however demonstrated for previous associated studies at these laboratories, at dietary levels between 1 and 800 ppm (LSR Schedule Nos. RHA/298/46030 and RHA/299/46030).

4. METHODS

4.1 Design conditions

4.1.1 Animals

Thirty-two male and thirty-two female CD rats were obtained from Charles River (UK) Limited, Margate, Kent, England. They were approximately three to four weeks of age on arrival and four days after arrival, selected animals had bodyweights in the range 98 to 111 g (males) and 89 to 102 g (females).

4.1.2 Identification

After random allocation to groups each rat was assigned a number, unique within the study, and identified by a tail tattoo.

4.1.3 Acclimatisation

The rats were allowed to acclimatise to the management conditions described below for eight days before commencement of treatment, during which their health status was assessed by daily observation.

4.1.4 Environmental control

The animals were housed in one room, inside a barriered, limited-access, rodent facility. Personnel entering the facility were required to change into protective clothing and wash all exposed skin. A further overall, plastic overshoes and mask were put on before entering the room and gloves were worn when handling animals.

Before delivery of the animals the room was cleaned and fogged with an iodophore bactericide. All diet bags and equipment entering the facility were passed through a chamber in which their external surfaces were similarly treated.

The room was kept at positive pressure with respect to the outside and had its own supply of filtered, fresh air which was passed to atmosphere and not recirculated. Ventilation equipment was designed to provide approximately 15 air changes per hour and a 12-hour light : 12-hour dark cycle operated. Target values for temperature and humidity were 21°C and 55% RH respectively.

Maximum and minimum temperature and relative humidity were recorded daily; these records indicate no significant variations from target values.

Temperature and airflow sensors were connected to an audible and visual alarm, so that immediate action could be taken in the event of a ventilation failure or of temperature fluctuations outside the pre-set limits.

4.1.5 Animal accommodation

The rats were housed five of one sex per cage. Each cage consisted of a high density polypropylene body measuring 56 x 38 x 18 cm with a stainless steel mesh lid and floor (Type RC1 from North Kent Plastics Limited, Dartford, Kent, England). These were suspended above absorbent crêpe paper which was changed twice a week. Cages, cage-trays, food hoppers and water bottles were changed at appropriate intervals.

4.1.6 Diet and water supply

A commercially-available complete powdered rodent diet, ('Laboratory Animal Diet No. 2', Biosure, Manea, Cambridgeshire, England), was fed *ad libitum*. This was an expanded diet which was subsequently ground by the manufacturer. It contained no added antibiotic or other chemotherapeutic or prophylactic agent. Weighed amounts of diet were provided at intervals during each week to each cage.

Drinking water was taken from the public supply, controlled by the East Anglian Water Company, Lowestoft, Suffolk, and offered *ad libitum* to each cage in polyethylene bottles fitted with sipper tubes.

4.1.7 Contaminants control

Each batch of diet was analysed by the supplier for nutritional components and chemical and microbiological contaminants. At approximately six-month intervals the same potential contaminants were also investigated by a laboratory independent of the supplier.

The public water supply met the European Economic Community and the World Health Organisation International Standards. At approximately six-month intervals water was analysed, by a laboratory independent of the supplier, for selected chlorinated and organophosphorus pesticides, polychlorinated biphenyls, and lead and cadmium contaminants; it was also examined for coliform bacteria.

Results of these analyses did not provide evidence of contamination that might have prejudiced the study.

No contaminants of the diet or water supply, other than those covered by the analyses mentioned above, were specifically investigated. None, deemed potentially to interfere with or prejudice the outcome of the study, was considered likely to be present.

4.1.8 Allocation to treatment groups

On arrival the rats were assigned to cages according to a sequence of computer-generated random numbers determining group and cage numbers. All animals were weighed during the acclimatisation period. Four male and five female animals with bodyweights at the extremes of the weight range were discarded and replaced with spare animals from the same batch. The cage distribution was designed to minimise the effects of any spatially variable component of the environment. The distribution is presented in Figure 1.

4.1.9 Identity of treatment groups

Group and animal identity numbers related to treatment as follows:

Group	Treatment	Dietary concentration (ppm)	Cage numbers		Animal numbers	
			Male	Female	Male	Female
1	Control	0	1	6	1-5	26-30
2	M&B 46030	500	2	7	6-10	31-35
3	M&B 46030	750	3	8	11-15	36-40
4	M&B 46030	1000	4	9	16-20	41-45
5	M&B 46030	1500	5	10	21-25	46-50

Each cage was provided with a label bearing the LSR Schedule number of this study, the treatment and treatment level (as appropriate), the group number, the cage number, the identity number of the animals therein and their sex.

All remaining spare animals were discarded without necropsy.

4.2 Treatment

4.2.1 Formulation

The M&B 46030 was incorporated into the ground diet at the constant concentration for each group by the preparation of a pre-mix followed by serial dilution with further quantities of untreated diet. Initially the test substance was mixed manually with a small quantity of diet and this pre-mix milled in an ultracentrifugal mill fitted with a 2 mm screen. Further diet was added and mixed for 10 minutes in a small planetary mixer. The final amount of diet required was added to give a final concentration of 1500 ppm and mixing was continued for 15 minutes in a Hobart A200 mixer. The diet was divided for treatment of the high treatment level group and for the preparation of diet for the remaining groups by a serial dilution process.

On each occasion of diet preparation, a 100 g aliquot of each treatment diet was taken into sealed aluminium foil laminated sachets and stored at ambient temperature pending possible future analytical requirements. No such analyses were required and they were discarded after three months.

Batches of test diets were prepared freshly each week. After formulation, diets were sealed in transparent polyethylene bags and labelled to identify the appropriate treatment group.

4.2.2 Test substance balance

On each occasion that quantities of M&B 46030 were weighed out for test diet preparation, the stock container of test compound was weighed before the first and after the last removal of part of its contents. The reduction in the weight of the stock container was documented as an independent check that the correct total weight of the test compound had been used.

4.2.3 Administration

The M&B 46030 was administered continuously, via the diet, throughout the treatment period. The dietary concentration was maintained at a constant level for each treated group. Control rats received untreated diet of the same batch at the same frequency as treated rats.

A record of the amount of diet required for feeding and the weight actually used was maintained for each group on each occasion of administration. These records did not indicate any significant error of administration.

4.2.4 Duration of treatment

All surviving rats were killed after completion of two weeks of treatment. Necropsies were completed in one day.

4.3 Serial observations

4.3.1 Signs

All rats were inspected at least twice daily throughout the treatment period for evidence of reaction to treatment, ill-health or mortality. Any deviations from normal were recorded at the time in respect of nature and severity, date and time of onset, duration and progress of the observed condition, as appropriate.

Although the various examinations were not confined to specific aspects they were aimed at the particular features listed below:

Twice daily examinations for death, morbidity or evidence of systemic toxicity or ill-health, the first in the morning and the second in the afternoon, on full work days.

A detailed weekly examination including palpation.

Any abnormality on the cage or cage-tray paper was also recorded.

During the acclimatisation period, observations of the animals were recorded at least once per day.

4.3.2 Mortality

Severely debilitated animals were killed. All rats killed, or those which died, were subjected to the terminal observations outlined in Section 4.4, as appropriate. The circumstances of each death, relevant *ante mortem* history and all necropsy findings, were recorded in detail.

4.3.3 Food consumption

The quantity of food eaten by each cage of rats was calculated weekly by measurement of the amount of food given and that remaining in, or scattered from the food hoppers.

4.3.4 Water consumption

Water consumption was assessed by visual examination. Quantitative measurements were not carried out.

4.3.5 Bodyweight

Each rat was weighed on the day that treatment commenced, twice weekly throughout the treatment period and before necropsy.

4.3.6 Food conversion ratio

Food conversion ratios were calculated for each group at weekly intervals as the amount of food consumed per unit of bodyweight gain.

4.3.7 Achieved dosage

Achieved dosages were calculated weekly and are expressed as mg/kg bodyweight/day.

4.4 Terminal observations

4.4.1 Euthanasia

All rats were killed by carbon dioxide inhalation.

Each rat was subjected to a detailed necropsy, as described below, with the minimum of delay.

The sequence in which the animals were killed on completion of the treatment period was selected to allow satisfactory inter-group comparison.

4.4.2 Macroscopic pathology

The necropsy procedure included a review of the history of each animal and a detailed examination of the external features and orifices, the neck and associated tissues and the cranial, thoracic, abdominal and pelvic cavities and their viscera. The external and cut surfaces of the tissues and organs were examined as appropriate.

Before disposal of the carcase a senior prosector reviewed the necropsy report in detail.

4.5 Data processing

4.5.1 Definition of study week

For the *in vivo* phase the first experimental week was defined as the time elapsing between completion of the recording of bodyweights on the day treatment commenced (Day 0) and completion of recording of bodyweight on the seventh day following. The subsequent experimental week was of the same duration.

4.5.2 General data treatment

Group mean values were calculated from the individual values presented in the appendices unless otherwise specified below. Standard deviation (SD) was calculated as appropriate using the sample statistic. Group means and standard deviations are presented to the same level of accuracy as the individual values.

4.5.3 Food consumption

Group mean food consumption values were calculated as the total amount of food consumed by the group divided by the number of rat-days, multiplying the result by seven to provide a weekly value. Rat-days were calculated as the total number of rats alive in the group summed for each day during the week.

Total food intake values presented in Table 2 were generated from unrounded weekly values.

4.5.4 Bodyweight

Bodyweight change was calculated from the individual bodyweight changes of rats surviving the period.

4.5.5 Food conversion ratio

Food conversion ratios were calculated for each group from unrounded mean food consumption divided by the difference in unrounded mean bodyweights.

4.5.6 Achieved dosages

The values reported for achieved dosages of the test compound were calculated from the nominal dietary concentration (ppm) multiplied by the unrounded mean daily food consumption divided by the unrounded mean mid-period bodyweight (g). The overall mean achieved dosages were calculated from the rounded weekly values presented in Table 5.

4.5.7 Statistical analysis

The significance of inter-group differences in bodyweight change data were assessed by Student's 't'-test using a pooled error variance.

Unless otherwise indicated the means were not significantly different from controls, $P < 0.05$.

4.6 Archives

All raw data and samples pertaining to this study, except those generated in the course of any supplier's or Sponsor's analysis are stored in the archives of Life Science Research.

5. RESULTS

5.1 Signs (Appendix 2)

One male receiving 750 ppm and the majority of animals receiving 1000 or 1500 ppm that were killed *in extremis* were noted to have piloerection, hunched posture and spastic muscle reaction. A few of these animals were also underactive.

Salivation and gasping respiration before death were noted for one female receiving the highest concentration.

During the treatment period, red staining around the muzzle and head was noted among several animals receiving 500 or 750 ppm.

5.2 Mortality (Table 1; Appendices 2, 4A and 4B)

All animals receiving 1000 or 1500 ppm died or were killed *in extremis* during the first three days of treatment. Two males and four females receiving 750 ppm died during the first four days of the treatment period and one male receiving this concentration died during the second week of treatment. Two males and one female receiving 500 ppm died during the treatment period.

5.3 Food consumption (Table 2)

Food consumption of animals receiving 500 or 750 ppm was markedly lower than that of their controls. Animals receiving 1500 ppm consumed little food before death.

5.4 Bodyweight (Figures 2A and 2B; Table 3; Appendix 3)

Marked bodyweight loss before death was noted for all animals receiving 1000 or 1500 ppm. The majority of animals receiving 500 or 750 ppm lost bodyweight over the first four days of the treatment period. Thereafter, the growth performance of these animals was inferior to that of their controls. The overall bodyweight gain of animals receiving 500 or 750 ppm was markedly inferior to that of the controls.

5.5 Food conversion ratio (Table 4)

The overall efficiency of food utilisation, as deduced from the food conversion ratios, of animals receiving 750 ppm was markedly inferior and that of animals receiving 500 ppm was inferior to that of their respective controls. The early mortality of rats receiving 1000 or 1500 ppm precluded the generation of data for this parameter.

5.6 Achieved dosages (Table 5)

The overall achieved dosages for animals receiving 500 or 750 ppm ranged from 55 to 98 mg/kg/day respectively.

5.7 Macroscopic pathology (Tables 6A and 6B; Appendices 4A and 4B)

A number of macroscopic changes were noted among animals killed or dying during the treatment period. These included distension and abnormal contents of the stomach, facial and perineal staining and dark lungs.

There were no macroscopic changes noted for animals killed after two weeks of treatment.

6. DISCUSSION

Effects of treatment with M&B 46030, a trifluoromethyl pyrazole insecticide, were apparent at all dietary concentrations used in this study.

All animals receiving 1000 or 1500 ppm died or were killed in the first few days of treatment. Bodyweight losses, minimal food intake and signs of general ill-health were noted for the majority of these animals. The macroscopic observations at necropsy did not aid the identification of a target organ for toxicity.

The majority of animals receiving 750 ppm and three out of ten animals receiving 500 ppm also died. Initial bodyweight losses and inferior growth performance, food intake and food conversion efficiency were apparent among survivors at these concentrations.

7. CONCLUSION

Treatment of CD rats with M&B 46030 at concentrations of 500, 750, 1000 or 1500 ppm resulted in deaths at all dietary levels.

The maximum tolerated level of M&B 46030 among CD rats is less than 500 ppm.

FIGURE 1

Group, cage and animal distribution

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

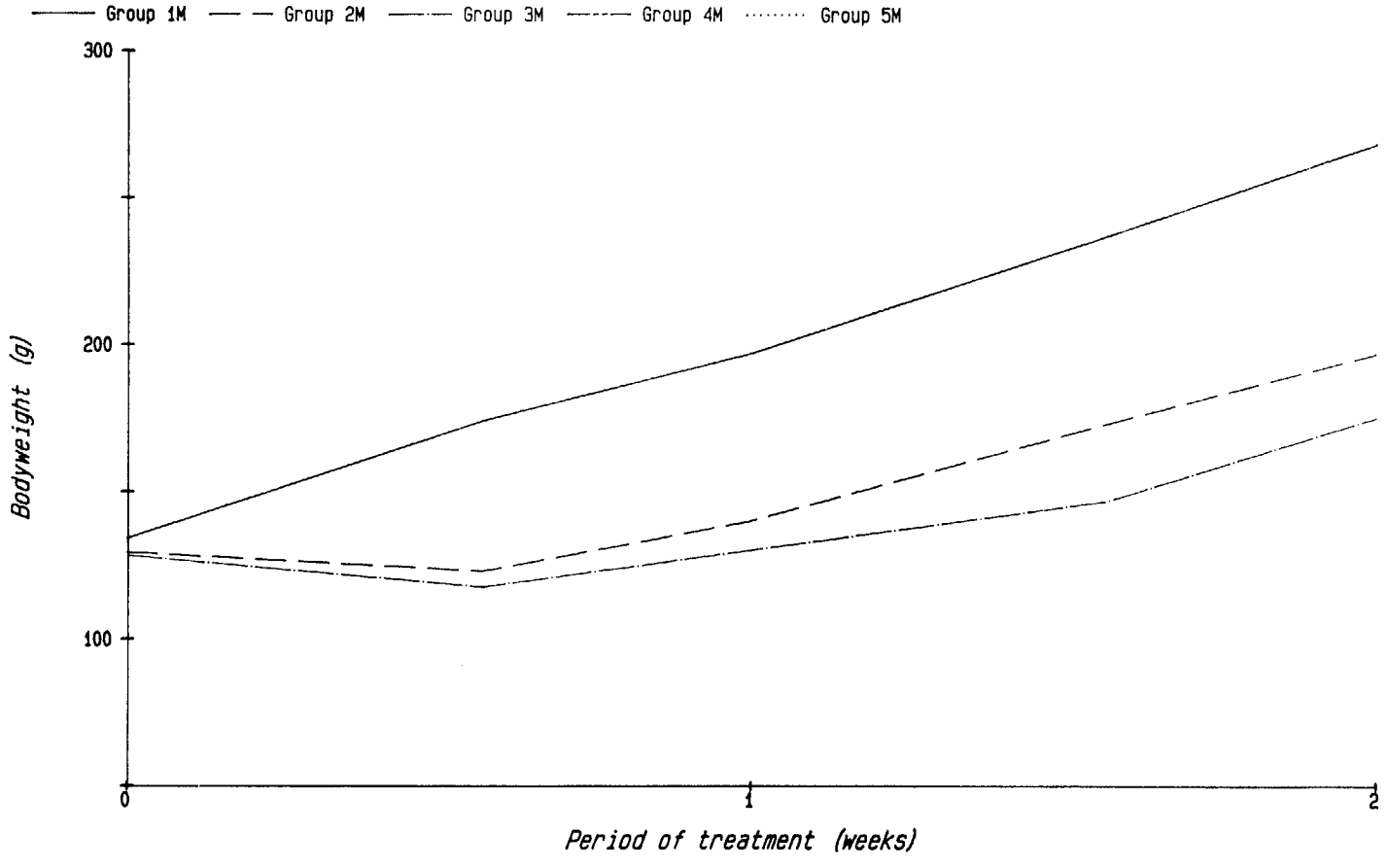
Cage number
Group number
Animal numbers

5 5 21-25	1 1 1-5	3 3 11-15
4 4 16-20	2 2 6-10	
6 1 26-30	9 4 41-45	10 5 46-50
7 2 31-35	8 3 36-40	

FIGURE 2A

Group mean bodyweight versus period of treatment - males

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

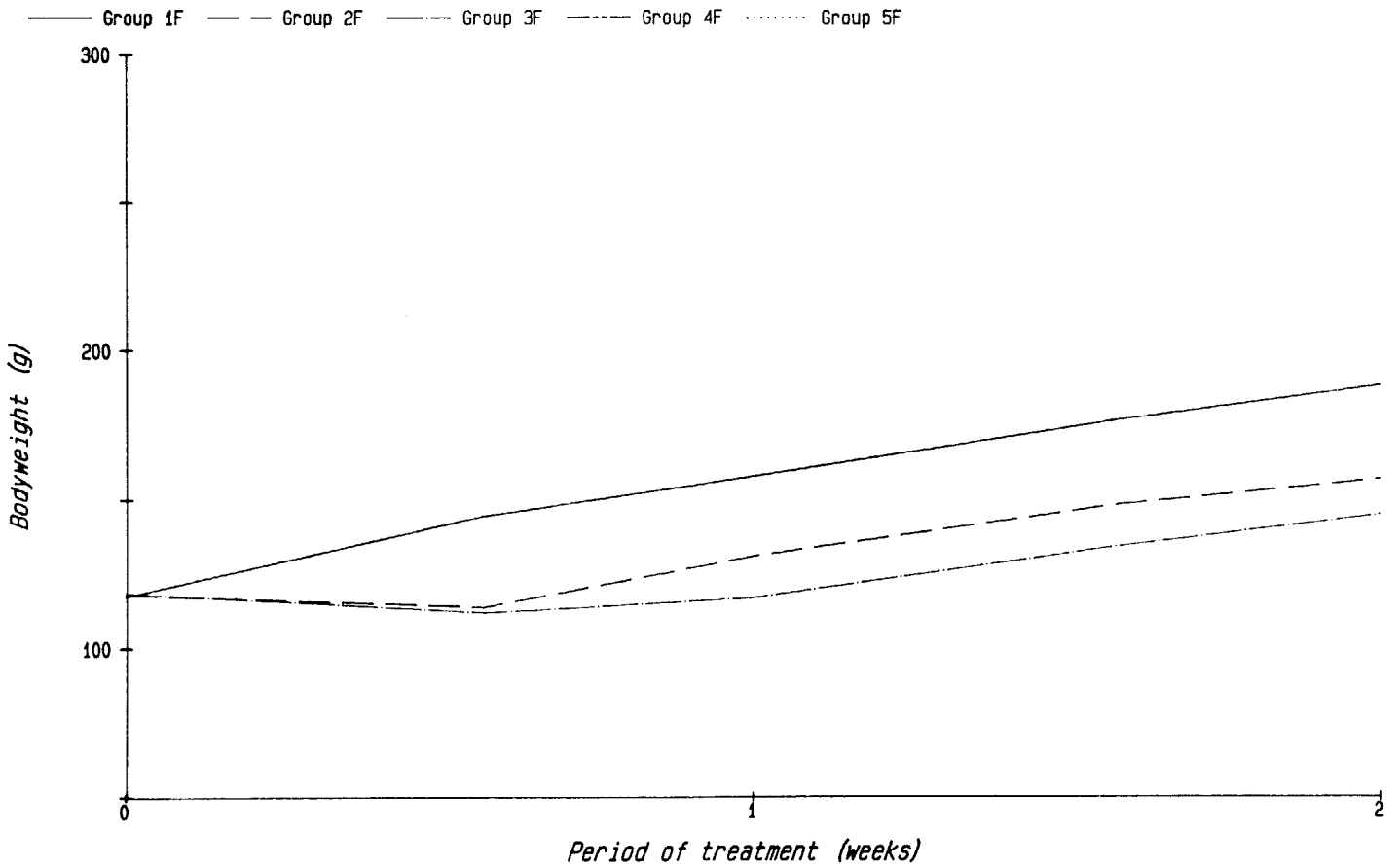


No Group 4 and 5 animal survived beyond Day 3 of treatment

FIGURE 2B

Group mean bodyweight versus period of treatment - females

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500



No Group 4 and 5 animal survived beyond Day 3 of treatment

TABLE 1

Daily incidence of mortality

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

	Group and sex									
Day	1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
2	0	0	0	2	5	0	0	0	2	5
3	0	1	0	3	0	0	1	2	3	0
4-9	0	0	2	0	0	0	0	2	0	0
10-11	0	1	0	0	0	0	0	0	0	0
12-14	0	0	1	0	0	0	0	0	0	0
Total	0	2	3	5	5	0	1	4	5	5

TABLE 2

Food consumption - group mean values (g/rat/week)

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Week number	Group and sex 1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
1	169	97	104			130	91	72*		
2	201	159	159			158	118	122		
Total 1-2	370	257	263	0	0	288	209	194	0	0
As % of control		69	71	-	-		73	67	-	-

* Only one animal surviving

TABLE 3

Bodyweight - group mean values (g)

Group	:	1	2	3	4	5
Compound	:	Control	------- M&B 46030 -------			
Level (ppm)	:	0	500	750	1000	1500

Day number	Group and sex 1M Mean	SD	2M Mean	SD	3M Mean	SD	4M Mean	SD	5M Mean	SD
0	134	5	129	4	128	7	133	4	134	5
4	174	8	123	8	118	17				
7	197	7	140	11	130	16				
11	237	13	173	15	147	24				
14	268	15	197	17	175	27				
Change										
0-4	40		-8[c]		-8[c]					
4-14	94		71[a]		49[c]					
0-14	134		66[c]		48[c]					
As % of control			49		36		-		-	

SD Standard deviation
a Significantly different from controls, $P < 0.05$
c Significantly different from controls, $P < 0.001$

TABLE 3 - continued

Bodyweight - group mean values (g)

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

	Group and sex									
Day	1F		2F		3F		4F		5F	
number	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
0	117	6	118	4	119	3	116	6	119	8
4	144	6	114	6	112*	-				
7	158	7	131	6	117	-				
11	176	9	148	2	134	-				
14	188	13	157	5	145	-				
Change										
0-4	27		-3[c]		-4[c]					
4-14	43		43		33					
0-14	70		40[c]		29[b]					
As % of control			57		41					

SD Standard deviation
b Significantly different from controls, $P < 0.01$
c Significantly different from controls, $P < 0.001$
* Only one animal surviving

TABLE 4

Food conversion ratio - group mean values

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Week number	Group and sex 1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
1	2.7	9.0	53.7	-	-	3.2	7.0	∞*	-	-
2	2.8	2.8	3.6	-	-	5.2	4.6	4.4	-	-
1-2	2.8	3.8	5.6	-	-	4.1	5.4	7.3	-	-

∞ Bodyweight loss or stasis
* Only one animal surviving

TABLE 5

Achieved dosage - group mean values (mg/kg/day)

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Week number	Group and sex 1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
1	-	51.28	87.07	-	-	-	52.80	65.76*	-	-
2	-	67.24	109.16	-	-	-	58.46	99.78	-	-
Mean	-	59.26	98.12	-	-	-	55.63	82.77	-	-

* Only one animal surviving

TABLE 6A

Macropathology - group distribution of findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030		-------
Level (ppm)	:	0	500	750	1000	1500

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Page: 1

Schedule number: RHA 422

		--- NUMBER OF ANIMALS AFFECTED ---									
	SEX:	----------MALE----------					---------FEMALE---------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN AND KEYWORD(S) OR PHRASE	NUMBER:	0	2	3	5	5	0	1	4	5	5
** TOP OF LIST **											
FOOT/FEET	NUMBER EXAMINED:	0	2	3	5	5	0	1	4	5	5
NON-SPECIFIC STAINING		0	0	1	0	0	0	0	0	0	0
LIVER	NUMBER EXAMINED:	0	2	3	5	5	0	1	4	5	5
APPEARS LARGE		0	0	1	0	0	0	0	0	0	0
LUNGS & BRONCHI	NUMBER EXAMINED:	0	2	3	5	5	0	1	4	5	5
DARK		0	1	1	2	4	0	0	1	0	4
INCOMPLETE COLLAPSE		0	1	1	0	2	0	0	0	0	2
FIRM		0	0	0	1	0	0	0	0	0	0
MISCELLANEOUS	NUMBER EXAMINED:	0	2	3	5	5	0	1	4	5	5
EMACIATED		0	0	1	0	0	0	0	0	0	0
PITUITARY	NUMBER EXAMINED:	0	2	3	5	5	0	1	4	5	5
DARK		0	0	0	1	0	0	0	0	0	0
SKIN	NUMBER EXAMINED:	0	2	3	5	5	0	1	4	5	5
PERINEAL STAINING		0	0	1	2	0	0	0	1	0	1
NON-SPECIFIC STAINING		0	0	0	1	0	0	1	0	1	2
FACIAL STAINING		0	0	3	3	5	0	1	3	3	2
STOMACH	NUMBER EXAMINED:	0	2	3	5	5	0	1	4	5	5
DISTENDED		0	1	0	2	5	0	0	1	2	2
ABNORMAL CONTENTS		0	0	0	0	4	0	0	0	2	0
APPEARS LARGE		0	0	0	0	0	0	0	0	0	2
TRACHEA	NUMBER EXAMINED:	0	2	3	5	5	0	1	4	5	5
ABNORMAL CONTENTS		0	0	0	1	2	0	0	0	0	0
** END OF LIST **											

TABLE 6B

Macropathology - group distribution of findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030		-------
Level (ppm)	:	0	500	750	1000	1500

Printed: 14-JAN-91
Page: 1

Schedule number: RHA 422

		--- NUMBER OF ANIMALS AFFECTED ---									
	SEX:	----------MALE---------					---------FEMALE--------				
	GROUP:	-1-	-2-	-3-	-4-	-5-	-1-	-2-	-3-	-4-	-5-
ORGAN AND KEYWORD(S) OR PHRASE	NUMBER:	5	3	2	0	0	5	4	1	0	0
** TOP OF LIST **											
FOOT/FEET	NUMBER EXAMINED:	5	3	2	0	0	5	4	1	0	0
LIVER	NUMBER EXAMINED:	5	3	2	0	0	5	4	1	0	0
LUNGS & BRONCHI	NUMBER EXAMINED:	5	3	2	0	0	5	4	1	0	0
MISCELLANEOUS	NUMBER EXAMINED:	5	3	2	0	0	5	4	1	0	0
PITUITARY	NUMBER EXAMINED:	5	3	2	0	0	5	4	1	0	0
SKIN	NUMBER EXAMINED:	5	3	2	0	0	5	4	1	0	0
STOMACH	NUMBER EXAMINED:	5	3	2	0	0	5	4	1	0	0
TRACHEA	NUMBER EXAMINED:	5	3	2	0	0	5	4	1	0	0
** END OF LIST **											

APPENDIX 1

Analysis of M&B 46030 - certificate from the Sponsor

The certificate of analysis for the batch of test compound used on this study is presented on the following pages.

CONFIDENTIAL

Copy No. 1527

D.Ag. No 5.

PHENYLPYRAZOLES: M&B 46,030:

Analysis of batch PGS 963 ex St. Fons, Lyon, France.

A Scientific Report from the Analytical Chemistry Laboratories

of

Rhône-Poulenc Agriculture Limited

by

G.C. Buddle, M.Sc., C.Chem., F.R.S.C.

and

W.Z. Jablonski

October, 1990

Rhône-Poulenc Agriculture Limited,
Fyfield Road,
Ongar,
Essex,
CM5 OHW,
England.

SUMMARY

1. A pilot scale batch of M&B 46,030, batch no. PGS 963 (ex St. Fons, France) has been examined by hplc, capillary g.c. and loss on drying.

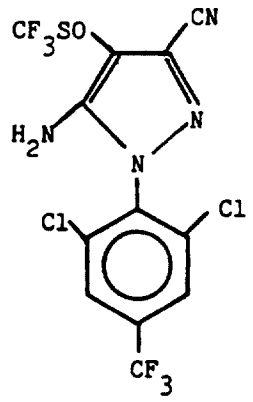
2. The assay of the material is 95.4% w/w. Impurities detected included:

M&B 45,950	=	0.23% w/w
M&B 46,136	=	3.03% w/w
3 unidentifieds	=	0.4% by peak area (total).

On the basis of present knowledge, the expiry date for this batch is set as November, 1992. However, this may be updated as the results of future retests become available.

1. INTRODUCTION

A pilot scale batch of M&B 46,030 has been prepared at St. Fons. An analysis of this was required to allow its use in Toxicology studies.



M&B 46,030

2. METHODS OF ANALYSIS

An hplc procedure has been developed for the assay of M&B 46,030[1]. This also allows the determination of 3 possible manufacturing impurities M&B 45,897, M&B 45,950 and M&B 46,136 (see Appendix I).

Additionally, this batch has been examined using a capillary g.c. procedure (see Appendix II) and for its loss on drying at 105°C.

3. RESULTS

3.1. Appearance — Creamy-yellow crystalline powder.

3.2. Assay — M&B 46,030, % w/w = 95.4.

3.3. Impurities

M&B 45,950, % w/w	=	0.23.
M&B 46,136, % w/w	=	3.03.
M&B 45,897, % w/w	=	none detected.

Other impurities, % peak area

RT = 3.2	=	0.23
RT = 4.08	=	0.16
RT = 4.75	=	0.03

Chromatogram of sample and standard solutions are shown in Figure 1.

3.4. Loss on Drying — % w/w = 0.02

3.5. Capillary g.c.

A capillary g.c. trace is shown in Figure 2. Area percentages are generally similar to figures calculated for % w/w for known impurities by hplc.

M&B 46,030	=	96.1%	peak area
M&B 45,950	=	0.35%	peak area
M&B 46,136	=	2.77%	peak area.

Two unidentifieds are also observed.

4. **CONCLUSION**

This batch of M&B 46,030, batch PGS 963, has been characterised for toxicology studies. A mass balance of ~99.2% has been achieved, which is considered acceptable.

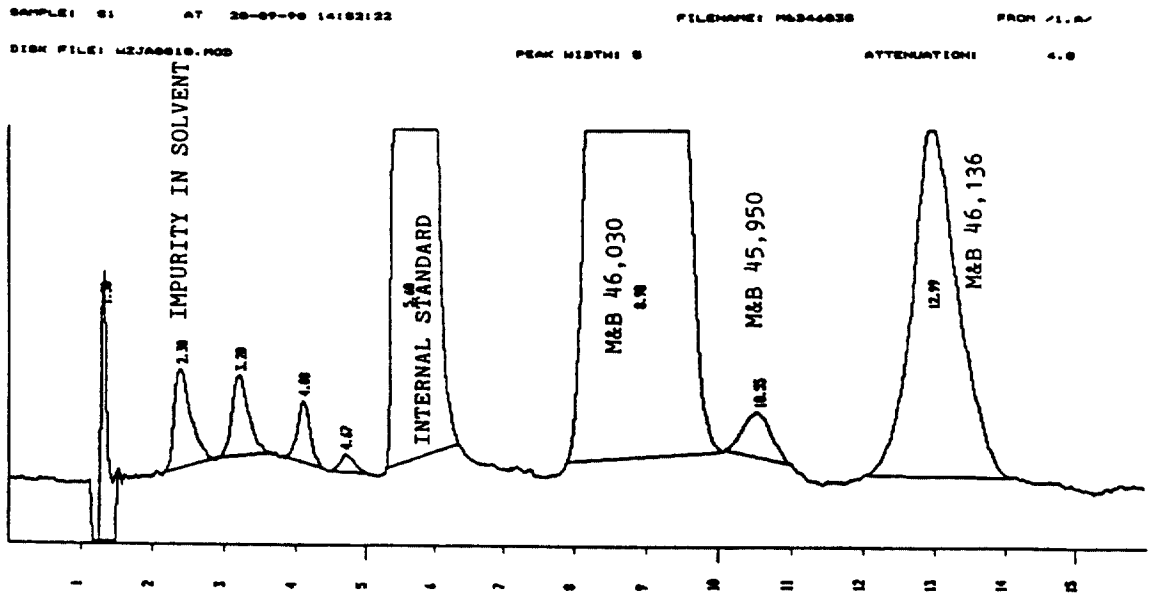
On the basis of current knowledge on this compound, an expiry date of November, 1992 is recommended for this batch stored at 20°C in the dark. This may be revised on the results of future retests of material.

5. **REFERENCE**

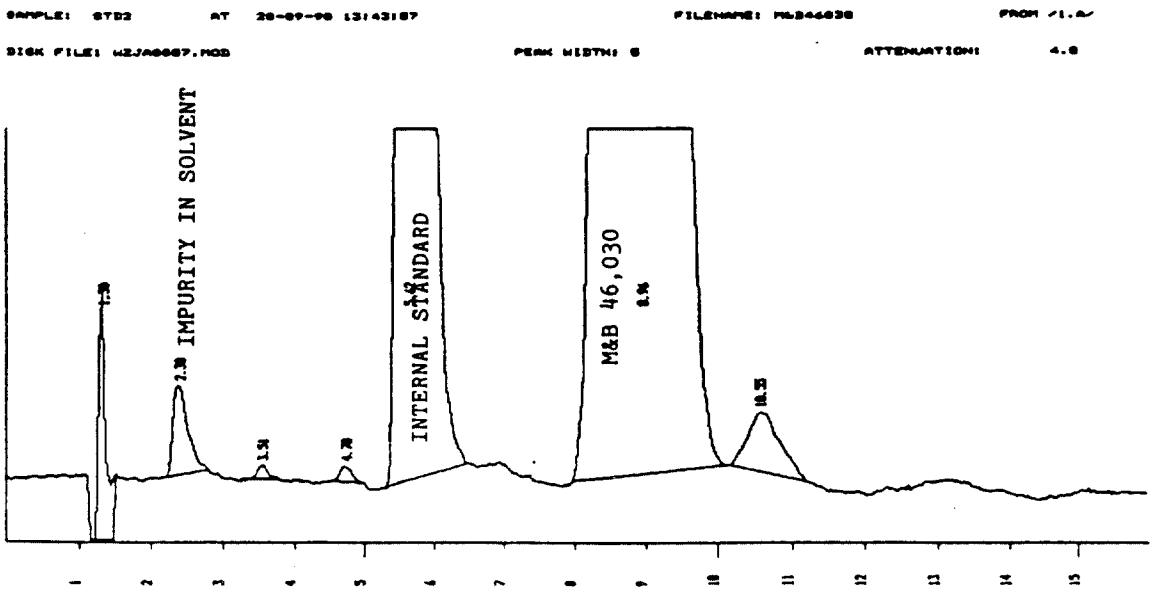
1. PHENYLPYRAZOLES: M&B 46,030: Hplc procedure for assay and impurities in the technical material. D.Ag. 1495, E.A.M. Mills, and G.C. Buddle, issued 16/8/90.

FIGURE 1 - Hplc Chromatograms of M&B 46,030

a) Batch PGS 963 (+ internal standard)



b) Reference sample (AJK 232) + internal standard



APPENDIX 1 - continued

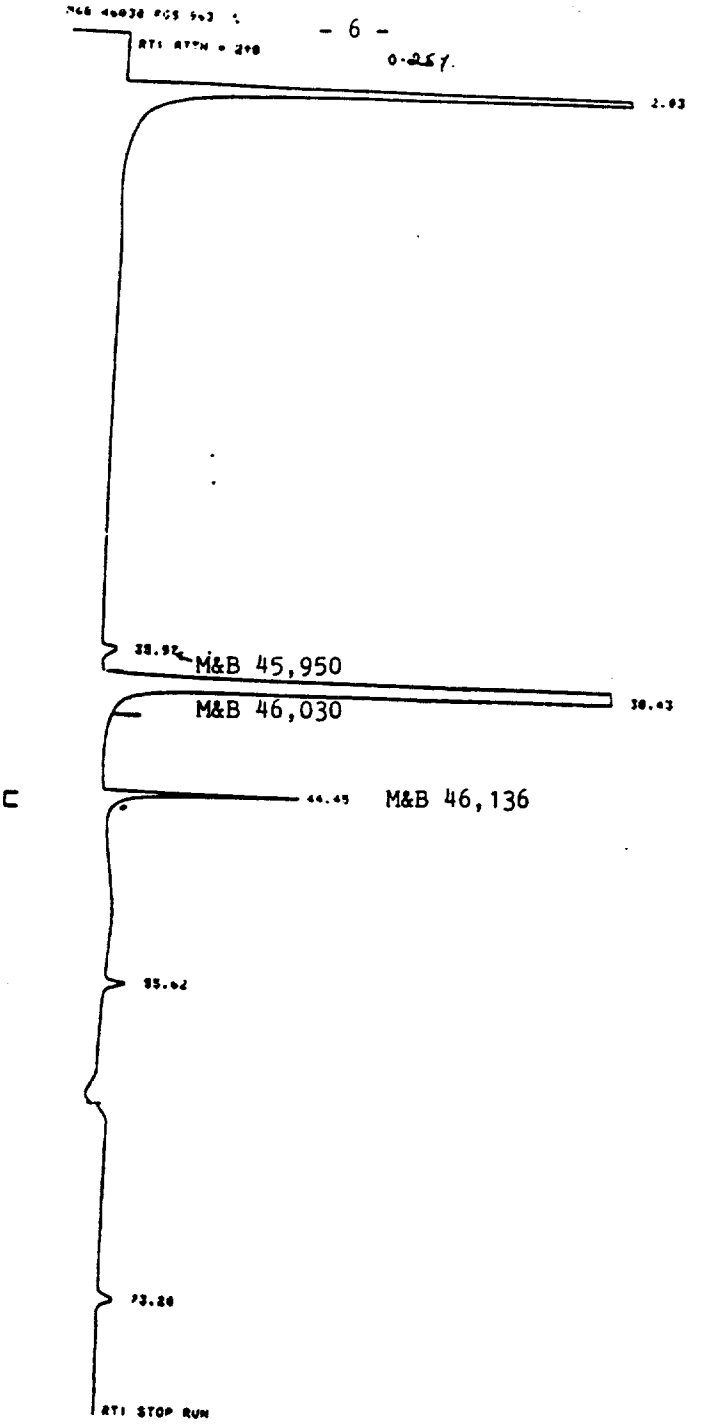


FIGURE 2 - Capillary . Chromatogram of M&B 46,030, batch 'S 963

Work carried out by:

9.10.90.

W.Z. Jablonski
(Analytical Development Chemist)

Work directed by:

9/10/90

G.C. Buddle, M.Sc., C.Chem., F.R.S.C.
(Section Head, Formulations Analysis)

Report prepared by:

9/10/90

G.C. Buddle, M.Sc., C.Chem., F.R.S.C.
(Section Head, Formulations Analysis)

Report approved by:

10/10/90

Dr. J.R. Outram, B.Sc., Ph.D., D.I.C.
(Analytical Chemistry Manager)

Date of Work:	September-October, 1990.
Notebook Number:	5818
Project Number:	P-90-320
Raw Data Storage:	Rhône-Poulenc GLP Archive, Ongar, Esssex.

- 8 -

QUALITY ASSURANCE COMPLIANCE

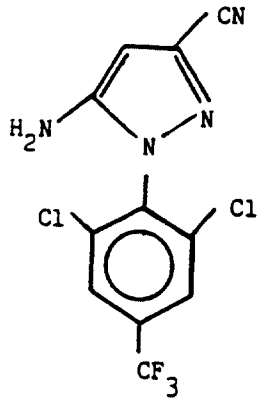
In an audit which was completed on 9/10/90 this report was found to describe accurately the methods and S.O.P.s used and to reflect accurately the results recorded in the raw data.

Signed: A Brentnall

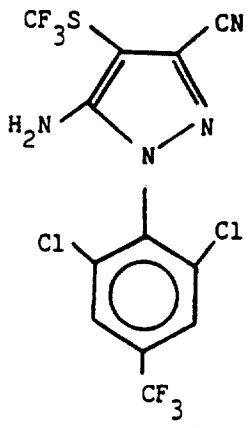
Quality Assurance (G.L.P.)

Dated: 10/10/90

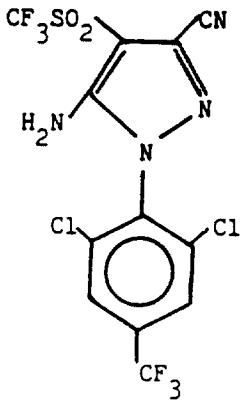
Appendix I - Structures of Manufacturing Impurities of M&B 46,030



M&B 45,897



M&B 45,950



M&B 46,136

Appendix II - Capillary g.c. Procedure for Impurity Profile

The following procedure has been developed to profile samples of M&B 46,030 technical. It is in the process of being fully validated for quantitative use and will be reported in due course.

G.C. Condition

Column:	Methyl silicone cross linked fused silica 50m x 0.3mm i.d., 0.52µ phase thickness.
Temperature programme:	150°C for 5 minutes, then 8°C/min to 190°C. Hold for 27 minutes, then 6°C/min to 270°C.
Detector temperature:	290°C.
Injector:	Cold on-column.
Carrier gas:	Helium, 2 ml/min.
Injection volume:	1µl.

Sample Solution

0.25% (or 0.1%) w/v in methanol.

APPENDIX 2

Fate of individual animals and signs observed at routine *in vivo* inspection

Group 1M : Control

Animal number	Death			Signs and weeks observed
	Week	Date	Mode	
1	3	06.09.90	Terminal kill	
2	3	06.09.90	Terminal kill	
3	3	06.09.90	Terminal kill	
4	3	06.09.90	Terminal kill	
5	3	06.09.90	Terminal kill	

APPENDIX 2 - continued

Fate of individual animals and signs observed at routine *in vivo* inspection

Group 2M : M&B 46030 : 500 ppm

Animal number	Death			Signs and weeks observed
	Week	Date	Mode	
6	2	01.09.90	Found dead	Muzzle staining 1. Dorsal hairloss 1.
7	1	25.08.90	Found dead	
8	3	06.09.90	Terminal kill	
9	3	06.09.90	Terminal kill	Dorsal hairloss 1.
10	3	06.09.90	Terminal kill	Muzzle staining 1. Dorsal hairloss 1.

APPENDIX 2 - continued

Fate of individual animals and signs observed at routine *in vivo* inspection

Group 3M : M&B 46030 : 750 ppm

Animal number	Death Week	Death Date	Death Mode	Signs and weeks observed
11	2	03.09.90	Found dead	Muzzle staining 1-2. Head staining 1. Thin 1-2. Hunched 1. Piloerection 1.
12	1	26.08.90	Found dead	
13	3	06.09.90	Terminal kill	Muzzle staining 1.
14	1	26.08.90	Found dead	
15	3	06.09.90	Terminal kill	Muzzle staining 1-2.

APPENDIX 2 - continued

Fate of individual animals and signs observed at routine *in vivo* inspection

Group 4M : M&B 46030 : 1000 ppm

Animal number	Death Week	Death Date	Mode	Signs and weeks observed
16	1	25.08.90	Killed *in extremis*	Muscle reaction spastic 1. Piloerection 1. Hunched 1.
17	1	24.08.90	Found dead	
18	1	25.08.90	Killed *in extremis*	Muscle reaction spastic 1. Piloerection 1. Hunched 1.
19	1	25.08.90	Killed *in extremis*	Muscle reaction spastic 1. Piloerection 1. Hunched 1.
20	1	24.08.90	Found dead	

APPENDIX 2 - continued

Fate of individual animals and signs observed at routine *in vivo* inspection

Group 5M : M&B 46030 : 1500 ppm

Animal number	Death			Signs and weeks observed
	Week	Date	Mode	
21	1	24.08.90	Found dead	
22	1	24.08.90	Killed *in extremis*	Head staining 1. Nasal staining 1. Muscle reaction spastic 1.
23	1	24.08.90	Found dead	
24	1	24.08.90	Found dead	
25	1	24.08.90	Killed *in extremis*	Muscle reaction spastic 1. Underactive 1. Nasal staining 1.

APPENDIX 2 - continued

Fate of individual animals and signs observed at routine *in vivo* inspection

Group 1F : Control

Animal number	Death			Signs and weeks observed
	Week	Date	Mode	
26	3	06.09.90	Terminal kill	
27	3	06.09.90	Terminal kill	
28	3	06.09.90	Terminal kill	
29	3	06.09.90	Terminal kill	
30	3	06.09.90	Terminal kill	

APPENDIX 2 - continued

Fate of individual animals and signs observed at routine *in vivo* inspection

Group 2F : M&B 46030 : 500 ppm

Animal number	Death			Signs and weeks observed
	Week	Date	Mode	
31	3	06.09.90	Terminal kill	Muzzle staining 1. Vocalisation 1.
32	3	06.09.90	Terminal kill	Dorsal hairloss 1.
33	3	06.09.90	Terminal kill	
34	3	06.09.90	Terminal kill	
35	1	25.08.90	Found dead	

APPENDIX 2 - continued

Fate of individual animals and signs observed at routine *in vivo* inspection

Group 3F : M&B 46030 : 750 ppm

Animal number	Death			Signs and weeks observed
	Week	Date	Mode	
36	1	26.08.90	Found dead	
37	3	06.09.90	Terminal kill	Muzzle staining 1.
38	1	27.08.90	Found dead	Muzzle staining 1.
39	1	25.08.90	Found dead	
40	1	25.08.90	Found dead	

APPENDIX 2 - continued

Fate of individual animals and signs observed at routine *in vivo* inspection

Group 4F : M&B 46030 : 1000 ppm

Animal number	Death Week	Death Date	Death Mode	Signs and weeks observed
41	1	24.08.90	Found dead	
42	1	25.08.90	Killed *in extremis*	Muscle reaction spastic 1. Piloerection 1. Hunched 1.
43	1	25.08.90	Found dead	
44	1	25.08.90	Killed *in extremis*	Muscle reaction spastic 1. Piloerection 1. Hunched 1.
45	1	24.08.90	Found dead	

APPENDIX 2 - continued

Fate of individual animals and signs observed at routine *in vivo* inspection

Group 5F : M&B 46030 : 1500 ppm

Animal number	Death			Signs and weeks observed
	Week	Date	Mode	
46	1	24.08.90	Killed *in extremis*	Piloerection 1. Underactive 1.
47	1	24.08.90	Killed *in extremis*	Muscle reaction spastic 1. Piloerection 1. Underactive 1.
48	1	24.08.90	Found dead	Salivation 1. Gasping 1. Muscle reaction spastic 1. Hunched 1. Dorsal staining 1.
49	1	24.08.90	Found dead	
50	1	24.08.90	Found dead	

APPENDIX 3

Bodyweight - individual values (g)

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Group / sex	Animal number	Day of treatment 0	4	7	11	14
1M	1	139	182	200	252	283
	2	126	162	184	216	243
	3	134	170	197	236	268
	4	134	176	201	240	274
	5	137	179	202	241	272
2M	6	132	116	135		
	7	124				
	8	126	117	133	163	182
	9	133	131	157	190	215
	10	132	128	136	166	193
3M	11	122	101	117	125	
	12	129				
	13	122	135	148	173	194
	14	137				
	15	132	117	126	143	156

APPENDIX 3 - continued

Bodyweight - individual values (g)

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Group / sex	Animal number	Day of treatment 0	4	7	11	14
4M	16	131				
	17	138				
	18	133				
	19	136				
	20	127				
5M	21	138				
	22	131				
	23	129				
	24	142				
	25	132				

APPENDIX 3 - continued

Bodyweight - individual values (g)

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Group / sex	Animal number	Day of treatment 0	4	7	11	14
1F	26	115	149	161	182	190
	27	116	143	164	177	180
	28	126	151	161	180	202
	29	121	144	156	181	198
	30	109	135	146	160	169
2F	31	114	107	126	151	160
	32	114	112	128	146	151
	33	121	122	139	147	155
	34	117	114	131	148	161
	35	124				
3F	36	121				
	37	116	112	117	134	145
	38	122				
	39	120				
	40	114				

APPENDIX 3 - continued

Bodyweight - individual values (g)

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Group / sex	Animal number	Day of treatment 0	4	7	11	14
4F	41	124				
	42	118				
	43	112				
	44	109				
	45	117				
5F	46	117				
	47	126				
	48	111				
	49	113				
	50	128				

APPENDIX 4A

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Printed: 14-JAN-91
Page: 1

Schedule number: RHA 422

ANIMAL NUMBER: 0006 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 01-SEP-90 STUDY DAY OF DEATH: 10 STUDY WEEK OF DEATH: 2 TERMINAL BODY WEIGHT: 146.1 GRAMS

* * * G R O S S P A T H O L O G Y O B S E R V A T I O N S * * *

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
LUNGS & BRONCHI (LL)		
	-DARK	
	-INCOMPLETE COLLAPSE	
STOMACH (ST)		
	-DISTENDED	-40X25X20MM, CONTAINING GAS AND FOOD MATERIAL.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0007 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 25-AUG-90 STUDY DAY OF DEATH: 3 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 117.0 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0011 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 03-SEP-90 STUDY DAY OF DEATH: 12 STUDY WEEK OF DEATH: 2 TERMINAL BODY WEIGHT: 126.6 GRAMS

*** GROSS PATHOLOGY OBSERVATIONS ***

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
FOOT/FEET (FE)		
	-NON-SPECIFIC STAINING	-BROWN STAINING ON MEDIAL SURFACES OF FOREPAWS.
LIVER (LI)		
	-APPEARS LARGE	-WT. 11.690G.
LUNGS & BRONCHI (LL)		
	-DARK	
	-INCOMPLETE COLLAPSE	
MISCELLANEOUS (ZO)		
	-EMACIATED	
SKIN (SK)		
	-PERINEAL STAINING	-YELLOW STAINING.
	-FACIAL STAINING	-RED/BROWN STAINING ON MUZZLE, LOWER JAW AND NARES.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0012 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 26-AUG-90 STUDY DAY OF DEATH: 4 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 121.0 GRAMS

* * * G R O S S P A T H O L O G Y O B S E R V A T I O N S * * *

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
SKIN (SK)		
	-FACIAL STAINING	-RED STAINING ON MUZZLE.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

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Schedule number: RHA 422

ANIMAL NUMBER: 0014 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 26-AUG-90 STUDY DAY OF DEATH: 4 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 117.7 GRAMS

ORGAN NAME	*** GROSS PATHOLOGY OBSERVATIONS *** SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
SKIN (SK)		
	-FACIAL STAINING	-BROWN STAINING ON MUZZLE.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0016 SEX: MALE DOSE GROUP: 4 SACRIFICE STATUS: UNSCHEDULED (K)
DATE OF DEATH: 25-AUG-90 STUDY DAY OF DEATH: 3 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 108.9 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0017 SEX: MALE DOSE GROUP: 4 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 24-AUG-90 STUDY DAY OF DEATH: 2 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 125.7 GRAMS

*** GROSS PATHOLOGY OBSERVATIONS ***

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
LUNGS & BRONCHI (LL)	-DARK	
SKIN (SK)	-PERINEAL STAINING	-YELLOW STAINING.
	-FACIAL STAINING	-RED/BROWN STAINING ON MUZZLE AND AROUND EYES. PALE YELLOW STAINING ON HEAD.
STOMACH (ST)	-DISTENDED	-40X25X20MM, CONTAINING FOOD MATERIAL.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0018 SEX: MALE DOSE GROUP: 4 SACRIFICE STATUS: UNSCHEDULED (K)
DATE OF DEATH: 25-AUG-90 STUDY DAY OF DEATH: 3 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 114.1 GRAMS

* * * G R O S S P A T H O L O G Y O B S E R V A T I O N S * * *

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
PITUITARY (PI)	-DARK	
SKIN (SK)	-FACIAL STAINING	-RED STAINING AROUND MOUTH.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0019 SEX: MALE DOSE GROUP: 4 SACRIFICE STATUS: UNSCHEDULED (K)
DATE OF DEATH: 25-AUG-90 STUDY DAY OF DEATH: 3 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 116.2 GRAMS

*** GROSS PATHOLOGY OBSERVATIONS ***

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
LUNGS & BRONCHI (LL)	-FIRM	
TRACHEA (TR)	-ABNORMAL CONTENTS	-CONTAINS PALE, AERATED FLUID.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0020 SEX: MALE DOSE GROUP: 4 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 24-AUG-90 STUDY DAY OF DEATH: 2 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 118.9 GRAMS

* * * GROSS PATHOLOGY OBSERVATIONS * * *

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
LUNGS & BRONCHI (LL)		
	-DARK	
SKIN (SK)		
	-PERINEAL STAINING	-YELLOW STAINING.
	-NON-SPECIFIC STAINING	-YELLOW STAINING ON DORSAL AND VENTRAL SURFACES.
	-FACIAL STAINING	-PALE YELLOW STAINING ON HEAD, MUZZLE AND AROUND EYES.
STOMACH (ST)		
	-DISTENDED	-40X25X20MM, CONTAINING FOOD MATERIAL.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0021 SEX: MALE DOSE GROUP: 5 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 24-AUG-90 STUDY DAY OF DEATH: 2 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 121.8 GRAMS

* * * GROSS PATHOLOGY OBSERVATIONS * * *

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
LUNGS & BRONCHI (LL)		
	-DARK	
SKIN (SK)		
	-FACIAL STAINING	-YELLOW/BROWN STAINING ON MUZZLE AND LOWER JAW.
STOMACH (ST)		
	-DISTENDED	-30X20X20MM.
	-ABNORMAL CONTENTS	-CONTENTS LIQUEFIED.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0022 SEX: MALE DOSE GROUP: 5 SACRIFICE STATUS: UNSCHEDULED (K)
DATE OF DEATH: 24-AUG-90 STUDY DAY OF DEATH: 2 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 114.0 GRAMS

* * * G R O S S P A T H O L O G Y O B S E R V A T I O N S * * *

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
LUNGS & BRONCHI (LL)		
	-DARK	
	-INCOMPLETE COLLAPSE	
SKIN (SK)		
	-FACIAL STAINING	-PALE, AERATED FLUID AROUND NARES. YELLOW STAINING ON HEAD.
STOMACH (ST)		
	-DISTENDED	-35X25X20MM.
	-ABNORMAL CONTENTS	-CONTENTS LIQUEFIED.
TRACHEA (TR)		
	-ABNORMAL CONTENTS	-CONTAINS PALE, AERATED FLUID.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0023 SEX: MALE DOSE GROUP: 5 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 24-AUG-90 STUDY DAY OF DEATH: 2 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 123.4 GRAMS

* * * GROSS PATHOLOGY OBSERVATIONS * * *

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
LUNGS & BRONCHI (LL)	-DARK	
SKIN (SK)	-FACIAL STAINING	-RED/BROWN STAINING ON MUZZLE.
STOMACH (ST)	-DISTENDED	-50X30X20MM.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0024 SEX: MALE DOSE GROUP: 5 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 24-AUG-90 STUDY DAY OF DEATH: 2 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 128.3 GRAMS

*** GROSS PATHOLOGY OBSERVATIONS ***

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
SKIN (SK)		
	-FACIAL STAINING	-RED STAINING ON MUZZLE AND LOWER JAW.
STOMACH (ST)		
	-DISTENDED	-35X20X20MM.
	-ABNORMAL CONTENTS	-CONTENTS LIQUEFIED.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0025 SEX: MALE DOSE GROUP: 5 SACRIFICE STATUS: UNSCHEDULED (K)
DATE OF DEATH: 24-AUG-90 STUDY DAY OF DEATH: 2 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 117.4 GRAMS

*** GROSS PATHOLOGY OBSERVATIONS ***

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
LUNGS & BRONCHI (LL)		
	-DARK	
	-INCOMPLETE COLLAPSE	
SKIN (SK)		
	-FACIAL STAINING	-BROWN STAINING ON MUZZLE.
STOMACH (ST)		
	-DISTENDED	-40X20X20MM.
	-ABNORMAL CONTENTS	-CONTENTS LIQUEFIED.
TRACHEA (TR)		
	-ABNORMAL CONTENTS	-CONTAINS PALE, AERATED FLUID.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0035 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 25-AUG-90 STUDY DAY OF DEATH: 3 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 111.0 GRAMS

*** GROSS PATHOLOGY OBSERVATIONS ***

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
SKIN (SK)		
	-NON-SPECIFIC STAINING	-YELLOW STAINING ON LIMBS, DORSAL AND VENTRAL SURFACES.
	-FACIAL STAINING	-BROWN STAINING AROUND MOUTH.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0036 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 26-AUG-90 STUDY DAY OF DEATH: 4 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: NOT ENTERED

*** GROSS PATHOLOGY OBSERVATIONS ***

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
MISCELLANEOUS (ZO)		
	-CANNIBALISED	-CAECUM, ILEUM AND JEJUNUM CANNIBALISED.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0038 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 27-AUG-90 STUDY DAY OF DEATH: 5 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: NOT ENTERED

* * * G R O S S P A T H O L O G Y O B S E R V A T I O N S * * *

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
LUNGS & BRONCHI (LL)		
	-DARK	
MISCELLANEOUS (ZO)		
	-CANNIBALISED	-HINDFEET, RIGHT FORELIMB, TAIL AND DORSAL CERVICAL REGION CANNIBALISED.
SKIN (SK)		
	-PERINEAL STAINING	-YELLOW STAINING.
	-FACIAL STAINING	-RED STAINING ON LOWER JAW, MUZZLE AND NARES.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0039 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 25-AUG-90 STUDY DAY OF DEATH: 3 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 113.0 GRAMS

* * * G R O S S P A T H O L O G Y O B S E R V A T I O N S * * *

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
SKIN (SK)		
	-FACIAL STAINING	-YELLOW STAINING.
STOMACH (ST)		
	-DISTENDED	-<50X23X20MM.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0040 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 25-AUG-90 STUDY DAY OF DEATH: 3 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 100.0 GRAMS

* * * GROSS PATHOLOGY OBSERVATIONS * * *

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
SKIN (SK)		
	-FACIAL STAINING	-YELLOW/BROWN STAINING AROUND MOUTH AND NARES.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0041 SEX: FEMALE DOSE GROUP: 4 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 24-AUG-90 STUDY DAY OF DEATH: 2 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 114.0 GRAMS

*** GROSS PATHOLOGY OBSERVATIONS ***

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
SKIN (SK)		
	-FACIAL STAINING	-PALE STAINING ON LOWER JAW AND RED/BROWN STAINING AROUND EYES.
STOMACH (ST)		
	-DISTENDED	-45X20X15MM.
	-ABNORMAL CONTENTS	-CONTENTS LIQUEFIED.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0042 SEX: FEMALE DOSE GROUP: 4 SACRIFICE STATUS: UNSCHEDULED (K)
DATE OF DEATH: 25-AUG-90 STUDY DAY OF DEATH: 3 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 102.6 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0043 SEX: FEMALE DOSE GROUP: 4 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 25-AUG-90 STUDY DAY OF DEATH: 3 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 100.0 GRAMS

*** GROSS PATHOLOGY OBSERVATIONS ***

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
SKIN (SK)		
	-FACIAL STAINING	-YELLOW/BROWN STAINING AROUND MOUTH AND NARES.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0044 SEX: FEMALE DOSE GROUP: 4 SACRIFICE STATUS: UNSCHEDULED (K)
DATE OF DEATH: 25-AUG-90 STUDY DAY OF DEATH: 3 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 95.4 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0045 SEX: FEMALE DOSE GROUP: 4 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 24-AUG-90 STUDY DAY OF DEATH: 2 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 106.5 GRAMS

*** GROSS PATHOLOGY OBSERVATIONS ***

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
SKIN (SK)		
	-NON-SPECIFIC STAINING	-RED STAINING ON MEDIAL SURFACES OF FORELIMBS.
	-FACIAL STAINING	-RED/BROWN STAINING ON MUZZLE, LOWER JAW AND NARES.
STOMACH (ST)		
	-DISTENDED	-30X15X15MM.
	-ABNORMAL CONTENTS	-CONTENTS LIQUEFIED.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0046 SEX: FEMALE DOSE GROUP: 5 SACRIFICE STATUS: UNSCHEDULED (K)
DATE OF DEATH: 24-AUG-90 STUDY DAY OF DEATH: 2 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 105.5 GRAMS

* * * G R O S S P A T H O L O G Y O B S E R V A T I O N S * * *

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
LUNGS & BRONCHI (LL)		
	-DARK	
	-INCOMPLETE COLLAPSE	
STOMACH (ST)		
	-APPEARS LARGE	-40X20X10MM.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0047 SEX: FEMALE DOSE GROUP: 5 SACRIFICE STATUS: UNSCHEDULED (K)
DATE OF DEATH: 24-AUG-90 STUDY DAY OF DEATH: 2 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 108.7 GRAMS

* * * G R O S S P A T H O L O G Y O B S E R V A T I O N S * * *

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
LUNGS & BRONCHI (LL)		
	-DARK	
	-INCOMPLETE COLLAPSE	
STOMACH (ST)		
	-APPEARS LARGE	-35X18X10MM.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0048 SEX: FEMALE DOSE GROUP: 5 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 24-AUG-90 STUDY DAY OF DEATH: 2 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 98.0 GRAMS

* * * GROSS PATHOLOGY OBSERVATIONS * * *

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
LUNGS & BRONCHI (LL)		
	-DARK	
SKIN (SK)		
	-NON-SPECIFIC STAINING	-YELLOW STAINING ON DORSAL SURFACE.
STOMACH (ST)		
	-DISTENDED	-45X30X10MM, CONTAINING FOOD MATERIAL.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0049 SEX: FEMALE DOSE GROUP: 5 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 24-AUG-90 STUDY DAY OF DEATH: 2 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 109.7 GRAMS

* * * G R O S S P A T H O L O G Y O B S E R V A T I O N S * * *

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
SKIN (SK)		
	-FACIAL STAINING	-RED/BROWN STAINING ON MUZZLE AND NARES.

APPENDIX 4A - continued.

Macropathology - individual findings for animals killed or dying during the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0050 SEX: FEMALE DOSE GROUP: 5 SACRIFICE STATUS: UNSCHEDULED (F)
DATE OF DEATH: 24-AUG-90 STUDY DAY OF DEATH: 2 STUDY WEEK OF DEATH: 1 TERMINAL BODY WEIGHT: 125.0 GRAMS

* * * G R O S S P A T H O L O G Y O B S E R V A T I O N S * * *

ORGAN NAME	SEVERITY, KEYWORD(S) OR PHRASE	FREE-TEXT COMMENTS AND NOTES
LUNGS & BRONCHI (LL)		
	-DARK	
SKIN (SK)		
	-PERINEAL STAINING	-YELLOW STAINING.
	-NON-SPECIFIC STAINING	-PALE STAINING ON MEDIAL SURFACES OF FORELIMBS.
	-FACIAL STAINING	-YELLOW STAINING ON LOWER JAW AND NARES.
STOMACH (ST)		
	-DISTENDED	-50X20X20MM, CONTAINING FOOD MATERIAL.

APPENDIX 4B

Macropathology - individual findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

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Schedule number: RHA 422

ANIMAL NUMBER: 0001 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06-SEP-90 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 280.3 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4B - continued.

Macropathology - individual findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0002 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06-SEP-90 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 239.7 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4B - continued.

Macropathology - individual findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0003 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06-SEP-90 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 265.2 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4B - continued.

Macropathology - individual findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0004 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06-SEP-90 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 271.9 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4B - continued.

Macropathology - individual findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0005 SEX: MALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06-SEP-90 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 270.8 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4B - continued.

Macropathology - individual findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0008 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06-SEP-90 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 175.7 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4B - continued.

Macropathology - individual findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0009 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06-SEP-90 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 210.2 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4B - continued.

Macropathology - individual findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0010 SEX: MALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06-SEP-90 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 187.7 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4B - continued.

Macropathology - individual findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0013 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06-SEP-90 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 190.5 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4B - continued.

Macropathology - individual findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0015 SEX: MALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06-SEP-90 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 154.9 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4B - continued.

Macropathology - individual findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0026 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06-SEP-90 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 185.5 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4B - continued.

Macropathology - individual findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0027 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06-SEP-90 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 177.3 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4B - continued.

Macropathology - individual findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0028 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06-SEP-90 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 198.2 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4B - continued.

Macropathology - individual findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0029 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06-SEP-90 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 193.2 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4B - continued.

Macropathology - individual findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

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Schedule number: RHA 422

ANIMAL NUMBER: 0030 SEX: FEMALE DOSE GROUP: 1 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06-SEP-90 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 166.6 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4B - continued.

Macropathology - individual findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0031 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06-SEP-90 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 155.7 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4B - continued.

Macropathology - individual findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0032 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06-SEP-90 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 147.5 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4B - continued.

Macropathology - individual findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0033 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06-SEP-90 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 153.1 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4B - continued.

Macropathology - individual findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0034 SEX: FEMALE DOSE GROUP: 2 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06-SEP-90 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 156.0 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

APPENDIX 4B - continued.

Macropathology - individual findings for animals killed after 2 weeks of the treatment period.

Group	:	1	2	3	4	5
Compound	:	Control	-------	M&B 46030	-------	
Level (ppm)	:	0	500	750	1000	1500

Schedule number: RHA 422

ANIMAL NUMBER: 0037 SEX: FEMALE DOSE GROUP: 3 SACRIFICE STATUS: SCHEDULED, TERMINAL SACRIFICE
DATE OF DEATH: 06-SEP-90 STUDY DAY OF DEATH: 15 STUDY WEEK OF DEATH: 3 TERMINAL BODY WEIGHT: 142.7 GRAMS

*** ANIMAL HAS NO GROSS OBSERVATIONS RECORDED ***

LSR Schedule No : RHA/422/46030
LSR Enquiry No : 4968A
Protocol Issue No : 1
No. of pages : 16

APPROVED PROTOCOL

M&B 46030 : PRELIMINARY TOXICITY STUDY BY DIETARY ADMINISTRATION TO CD RATS FOR FOUR WEEKS

Protocol prepared for

Rhône-Poulenc Agrochimie

by

Life Science Research Limited
Eye, Suffolk, IP23 7PX
England

30 July 1990

LSR Schedule No : RHA/422
LSR Enquiry No : 4968A
Protocol Issue No : 1

APPROVED PROTOCOL

PROTOCOL DEVELOPMENT : Cumulative history

Issue No.	Date sent to Sponsor	Actions and responses
1	31 July '90	

A signed copy of this protocol was received by facsimile from the Sponsor on 14 August 1990. The fax document was signed by the Study Director on this date and used as the working protocol for the study.

PA 23 August '90.

MANAGEMENT OF STUDY

Project Co-ordinator : W. Davies, B.Sc., M.Sc., Ph.D., Dip.R.C.Path.

Study Director : P. Aughton, B.Sc., C.Biol., M.I.Biol.

Sponsor : Rhône-Poulenc Agrochimie
14-20 rue Pierre Baizet
B.P. 9163
69263 Lyon Cedex 09
France

Monitor : Mr B. Ingham

Executive monitor : Dr C. Silice

Project licence : 70/00710. Repeat dose toxicology and oncology (procedure ref. No. 17)

Project licensee : S.J. Amyes, Ph.D.

LSR Schedule No : VRHA/422
LSR Enquiry No : 4968A
Protocol Issue No : 1

PROTOCOL APPROVAL

APPROVED PROTOCOL

For LIFE SCIENCE RESEARCH LIMITED

Issued by : _____ Date : 31 July '90

Released by : _____ Date : 31 July 1990

For RHONE-POULENC AGROCHIMIE

(Please read Sections A and B, and complete the appropriate section. Please note that the study cannot begin unless Life Science Research Limited is in receipt of a protocol signed in Section A)

A. STUDY TO BE CONDUCTED USING THIS PROTOCOL

This document is the working protocol for the study and will be reproduced in the final report. Any modifications that are required have been made on the document, and have been initialled and dated. These, and any changes made subsequent to the date of my signature below, will be documented in formal amendments.

Approved by : _____ Date : 13/8/90
(for RHONE-POULENC AGROCHIMIE)

Please note

To comply with Good Laboratory Practice, and to allow the study to be conducted correctly and in a timely manner, it is VERY IMPORTANT that:

i) All changes to the protocol are clearly identifiable, intelligible and legible. The original content should not be obscured.

ii) The protocol is returned to Life Science Research Limited as soon as possible, and certainly before the proposed start date for the study.

STUDY DIRECTOR

The Sponsor has approved the initiation of the study according to the procedures described in this document. I have read and agreed the contents of this document and authorise its distribution.

Study Director : _____ Date : 23 August '90
(for LIFE SCIENCE RESEARCH LIMITED)

B. STUDY NOT TO BE STARTED. MODIFICATIONS REQUIRED

This protocol requires revision and may not be used to initiate the study. A further issue of the protocol must be prepared and signed on behalf of the Sponsor before the study may start.

Reviewed by : _____ Date : _____
(for RHONE-POULENC AGROCHIMIE)

LSR Schedule No : RHA/422
LSR Enquiry No : 4968A
Protocol Issue No : 1

APPROVED PROTOCOL

M&B 46030 : PRELIMINARY TOXICITY STUDY BY DIETARY ADMINISTRATION TO CD RATS FOR FOUR WEEKS

1. Introduction

1.1 Objective

The toxic effects of M&B 46030 will be assessed, in a four week feeding study in rats (two weeks if overt signs of effects are evident), to aid the selection of dosages for a combined oncogenicity and toxicity study in this species (LSR Schedule No. RHA/312/46030). The procedures detailed in the protocol will be performed to current, internationally recognised Good Laboratory Practice standards.

1.2 Choice of animal model

The rat has been chosen because of its use in the main study as a predictor of neoplastic and toxic change in man and the requirement for a rodent species by regulatory agencies. The CD strain will be used because of the historical control data available in this laboratory and its established susceptibility to known carcinogens.

1.3 Choice of route of administration and dietary concentrations

Oral administration has been selected to accord with the major potential route of exposure in manufacture and use; for convenience the test substance will be administered by admixture with the diet. Dietary concentrations of 500, 750, 1000 and 1500 ppm have been selected by the Sponsor.

1.4 Safety precautions

The precautions necessary when handling either the test substance or prepared formulations of the test substance will be based on information supplied by the Sponsor. The minimum safety precautions necessary will be detailed under the LSR hazard class 3 (to be up-dated, if required, in an amendment to the protocol).

LSR Schedule No : RHA/422
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APPROVED PROTOCOL

1.5 Location of study : Life Science Research Limited
Eye
Suffolk IP23 7PX
England

Tel: (0379) 644122
Telex: 975 389 LIFSCI G
Fax: (037971) 427

2. Scheduled time plan (to be up-dated as required in an amendment to the protocol)

Sample of M&B 46030 to arrive	:	
Animals to arrive	:	15 August 1990
Treatment to commence	:	w/b 20 August 1990
Terminal sacrifice to commence*	:	w/b either 3 September 1990 or 17 September 1990
Summary of results to Sponsor*	:	w/b either 17 September 1990 (estimated) or 1 October 1990 (estimated)
Draft report to be issued	:	November 1990 (estimated)

* Date depends on study duration, either two weeks (if overt effects are evident within this time) or four weeks

3. Animal management

3.1 Animals

Rats of the CD strain (ordered at 21 to 28 days of age, 60 to 80 g bodyweight) will be obtained from Charles River (UK) Limited, Margate, Kent, England.

If the animals are considered unsuitable for any reason, all animals will be replaced (no extra cost to Sponsor).

3.2 Pre-commencement animal replacement

Ten spare animals will be ordered to replace any individuals rejected during the acclimation period using the following criteria:

i) signs of ill-health or abnormalities

ii) extremes of the bodyweight range

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If the number of animals required for i) exceeds that supplied as spares the Sponsor will be advised and all animals will be replaced as indicated in Section 3.1.

3.3 Identification

After random allocation to groups (Section 3.9) each rat will be assigned a number and identified uniquely within the study by a tail tattoo.

3.4 Acclimation

The rats will be allowed to acclimate to the husbandry conditions described below for at least seven, but not more than fourteen, days before commencement of treatment; they should not be more than six-weeks old at the start of treatment. During the acclimation period their health status will be assessed from daily observations.

3.5 Environmental control

Rats will be housed inside a barriered rodent facility.

Each animal room is kept at positive pressure with respect to the outside by its own supply of filtered fresh air which is passed to atmosphere and not re-circulated. Target values within the animal rooms are 21°C for temperature, 55% for relative humidity and at least 15 air changes per hour. Lighting is controlled to provide a 12-hour light : 12-hour dark cycle.

The facility is designed and operated to minimise the entry of external biological and chemical agents and to minimise the transference of such agents between rooms. Before and after each study the room is cleaned and disinfected with a bactericide.

Access is limited to authorised personnel who are required to wash or shower and change into clean protective clothing. Where practicable, materials and equipment enter the facility through an autoclave or a chamber in which their external surfaces are treated with a bactericide.

Alarms are activated if the ventilation system fails, or temperature limits are exceeded. Periodic checks are made on the number of air changes in the animal rooms. Temperature and humidity are monitored daily. These data will be retained in the archives.

A stand-by electricity supply will automatically be brought into operation should the public supply fail.

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3.6 Animal accommodation

The rats will be housed five of one sex per cage, unless this number is reduced by mortality or isolation (Section 5.2). The cages used will be Type TR18 (Modular Systems Limited, London, England), which are made of a stainless steel body measuring 51 x 38 x 20 cm with a stainless steel mesh lid and floor. The cages will be suspended above absorbent crêpe paper. The latter will be changed three times a week; cages, cage-trays, food hoppers and water bottles will be changed at appropriate intervals.

3.7 Diet and water supply

A commercially-available powdered rodent diet, LAD2 (Biosure, Manea, Cambridgeshire, England), will be available *ad libitum*. This is an expanded diet which is subsequently ground by the manufacturer. It contains no added antibiotic or other chemotherapeutic or prophylactic agent. Weighed amounts of diet will be provided at intervals during each week to each cage.

At the end of each treatment week the weight of uneaten food will be recorded and the food discarded.

Water will be available *ad libitum* via polyethylene or polycarbonate bottles with sipper tubes.

3.8 Analysis of basal diet and water

Each batch of diet is routinely analysed by the supplier for various nutritional components and chemical and microbiological contaminants. At approximately six-month intervals the potential contaminants investigated by the supplier will also be analysed by a laboratory independent of the supplier.

Water will be taken from the public supply (East Anglian Water Company), which meets the European Economic Community and the World Health Organisation International Standards. At approximately six-month intervals water is routinely analysed, by a laboratory independent of the supplier, for selected chlorinated and organophosphorus pesticides, polychlorinated biphenyls, and lead and cadmium contaminants; it is also examined for coliform bacteria.

Results of all analyses will be retained in the archives.

No other specific contaminants, likely to be present in the diet or water, are known that may interfere with or prejudice the outcome of the study. Any such contaminants notified by the Sponsor before or during the study will be documented in an amendment to the protocol and analysed, if requested by the Sponsor.

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3.9 Allocation to treatment groups

On arrival animals will be assigned to cages using a set of computer-generated random numbers, resulting in a random allocation of animals to treatment groups. All animals will be weighed during the acclimation period; animals at the extremes of the weight distribution will be discarded and replaced with surplus animals selected from the same batch. Animals of the same sex may be interchanged between cages in order to achieve approximately equal mean bodyweights for each group at the commencement of treatment.

As far as is practicable the cage distribution will be designed to minimise the effect of any spatially variable component of the environment. The distribution will be documented in the final report.

4. Treatment

4.1 Identity of treatment groups (to be selected from 60 rats ordered)

Group	Treatment	Dietary concentration (ppm)	Cage numbers		Animal numbers	
			Male	Female	Male	Female
1	Control	0	1	6	1-5	26-30
2	M&B 46030	500	2	7	6-10	31-35
3	M&B 46030	750	3	8	11-15	36-40
4	M&B 46030	1000	4	9	16-20	41-45
5	M&B 46030	1500	5	10	21-25	46-50

Cage labels, identifying the occupants by experiment, animal number, sex and treatment group will be colour-coded; white labels will denote animals not assigned to study groups.

All remaining spare animals will be removed from the study room on the first day of treatment.

4.2 Test substance

Before use the identity, strength, purity and composition, or other characteristics which appropriately define the batch from which the test substance for this study is to be drawn, will be determined by the Sponsor. Stability of the test substance and methods of synthesis, fabrication or derivation will be documented by the Sponsor.

The test substance will be stored at ambient temperature or in a cool store (not exceeding 15°C) and protected from light.

In order to demonstrate the integrity of the test substance under the conditions in which it is to be stored at these laboratories, a single 2 g sample will be returned to the Sponsor every six months for reanalysis throughout, and on completion of, the programme of work using this test substance. Results of these analyses will be communicated to LSR for inclusion in the relevant final report.

Before any consignment of the test substance is used in the programme of work at these laboratories, the Pharmacy Department of LSR will ensure that a 2 g representative sample has been taken. This sample will be placed in a well-closed glass container, stored under the conditions specified for the bulk supply of the test substance and retained in the archives.

Similar procedures will be adopted for any additional consignments of the test substance used during the course of the programme.

4.3 Formulation

The M&B 46030 will be incorporated into the ground diet to provide the required dietary concentrations throughout the treatment period by initial preparation of a premix, followed by dilution with further quantities of the diet and mixing in an electrically grounded (earthed) mixer. Batches of each test diet will be prepared each week and issued in sealed polyethylene bags. The unused residue at the end of each week will be discarded.

If test diet samples are required for quality control purposes (see Section 4.4), 100 g aliquots of each test diet will be sealed in aluminium foil laminate sachets and stored in a refrigerator (approximately 4°C) pending possible future analytical requirements or until the approved final report has been issued. The samples will then be either sent to the Sponsor or destroyed, as directed by the Sponsor.

On all other occasions, 100 g aliquots of each test diet will be sealed in aluminium foil laminate sachets and stored at ambient temperature. In the event of an unexpected reaction by the animals, the aliquots from the diets fed during the period in which the reaction occurred will be analysed. The unused aliquots will be discarded after three months.

4.4 Quality control of dosage form

On each day that quantities of test substance are to be weighed out for test diet preparation, the stock container of test substance will be weighed before the first and after the last removal of part of its contents. The reduction in the weight of the stock container will be documented as a check that the required amount of the test substance has been used.

Before commencement of treatment the suitability of the proposed mixing procedure will be determined by a trial preparation. The details of the mixing procedure will be documented for inclusion in the final report.

Investigations of stability, homogeneity and achieved concentration of test diets, either before or during the treatment period, will only be performed if requested by the Sponsor. Any such request will be documented in an amendment to the protocol.

4.5 Administration

The test substance will be administered continuously via the diet. The dietary concentration will be maintained at a constant for each group throughout the treatment period.

Animals will not have access to mixed diet beyond the end of its shelf-life as determined by the stability test (if performed). Control rats will receive untreated diet at the same frequency, and from the same batch, as treated animals.

4.6 Scheduled duration of treatment

Treatment will be continuous for either two weeks (if overt effects are evident within this time) or four weeks (if no overt effects are seen in the first two weeks of treatment). The treatment period may be extended beyond four weeks in order to investigate any equivocal or progressive effects.

Throughout any additional period, including the necropsy period, treatment will be continued for all surviving animals. The serial observations will be recorded at the appropriate intervals described below (Section 5).

Data pertaining to any additional complete weeks before commencement of the necropsies will be included in the final report.

5. Serial observations

5.1 Signs

Rats and their cage-trays will be inspected at least twice daily for evidence of reaction to treatment or ill-health. Any deviations from normal will be recorded at the time in respect of nature and severity, date and time of onset, duration and progress of the observed condition, as appropriate.

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The observations are designed to identify abnormalities in, at least, the following:

Skin and fur
Eyes and mucous membranes
Respiratory system
Circulatory system
Autonomic and central nervous system
Somatomotor activity
Behaviour pattern

In addition the animals will be palpated once each week. The outcome of this examination will be documented.

During the acclimation perioo, observations of the animals and their cage-trays will be recorded at least once per day.

5.2 Mortality

Debilitated animals will be observed carefully and may be isolated to prevent cannibalism. Animals may be killed for humane reasons. Animals judged to be *in extremis* will be killed.

Rats found dead outside the normal work-day will be preserved in a refrigerator (approximately 4°C) provided for this purpose. A necropsy will be performed as soon as possible the following day.

A complete necropsy will be performed in all cases as described in Section 6 below.

5.3 Food consumption

The weight of food supplied to each cage, that remaining and an estimate of the amount spilled will be recorded for each week throughout the treatment period. From these records the mean weekly consumption per rat will be calculated for each cage.

5.4 Water consumption

Water consumption measurements may be instituted, and documented for inclusion in the final report, if any observations suggest a treatment-related effect on body fluids balance.

5.5 Bodyweight

Each animal will be weighed on the day that treatment commences, twice weekly throughout the treatment period and before necropsy.

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More frequent weighings may be instituted for animals displaying ill-health so that the progress of the observed condition can be monitored. These data will be retained in the archives.

5.6 Food conversion ratio

The group mean food conversion ratios of each sex, expressed as the weight of food consumed per unit gain in bodyweight, will be calculated for each week of treatment.

5.7 Achieved dosage

The group mean achieved dosage for each sex, expressed as mg/kg/day, will be calculated for each week of treatment. This will be calculated from the appropriate dietary test substance concentration, food consumption and bodyweight data.

6. Terminal observations

6.1 Euthanasia

Animals sacrificed during the study and those surviving until the end of the scheduled treatment period will be killed by carbon dioxide inhalation.

The sequence in which the animals are killed after completion of treatment will be selected to allow satisfactory inter-group comparison.

6.2 Macroscopic pathology

All animals killed and any found dead will be subjected to a detailed necropsy.

The necropsy procedure will include a review of the history of each animal and a detailed examination of the external features and orifices, the neck and associated tissues and the cranial, thoracic, abdominal and pelvic cavities and their viscera. The requisite organs will be weighed and external and cut surfaces of the organs and tissues will be examined as appropriate. Abnormalities and interactions will be noted and the required tissue samples preserved in fixative (see below).

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Before disposal of the carcase the retained tissues will be checked against the protocol and a senior prosector will review the necropsy report.

Representative photographs will be taken of any significant findings if considered appropriate.

6.3 Organ weights

The organs will be dissected free of adjacent fat and other contiguous tissue and the weights recorded as specified in the Pathology Procedures Table. The ratio of organ weight to bodyweight (recorded immediately before necropsy) will be calculated for each rat surviving until the end of the scheduled treatment period.

Delete 6.3 + 6.4 + relevant list on p 14 NGC

6.4 Tissues preserved in fixative

Samples of the tissues specified in the Pathology Procedures Table will be preserved in buffered 4% formaldehyde saline, except eyes, optic nerves and Harderian glands which will be placed in Davidson's fluid. Bone marrow smears, taken from all animals killed, will be air-dried and fixed in methanol.

In those cases where a lesion is not clearly delineated, contiguous tissue will be fixed with the grossly affected region as appropriate. The preserved tissues will be held against possible future requirements for microscopy.

Histological processing and microscopic examination of the retained tissues will only be performed, and documented in an amendment to the protocol, if requested by the Sponsor.

7. Data treatment

7.1 Statistical analysis

Standard deviations will be calculated as considered appropriate.

Details of any statistical tests used and the data to which they apply will be included in the final report.

APPROVED PROTOCOL

LSR Schedule No : RHA/422
LSR Enquiry No : 4968A
Protocol Issue No : 1

PATHOLOGY PROCEDURES

TISSUE	WEIGH	FIX
Abnormalities	if poss	*
Adrenals	L+R	L+R
Aorta (thoracic)		*
Brain	*	*
Caecum		*
Colon		*
Duodenum		*
Epididymides		L+R
Eyes and optic nerves		L+R
Femoral bone and marrow		*
Harderian glands		L+R
Heart	*	*
Ileum		*
Jejunum		*
Kidneys	L+R	L+R
Liver	*	*
Lungs (with mainstem bronchi)	*	*
Lymph nodes (mandibular)		*
(mesenteric)		*
Mammary glands (caudal)		*
(cranial)		*
Marrow smear		*
Oesophagus		*
Ovaries	L+R	L+R
Pancreas		*
Pituitary	*	*
Prostate	*	*
Rectum		*
Salivary glands (submandibular)		L+R
Sciatic nerves		L+R
Seminal vesicles		*
Skeletal muscle (thigh)		*
Skin		*
Spinal cord		*
Spleen	*	*
Sternum		*
Stomach (keratinised)		*
(glandular)		*
Testes	L+R	L+R
Thymus	*	*
Thyroid (with parathyroids)§	L+R	L+R
Tongue		*
Trachea		*
Urinary bladder		*
Uterus with cervix	*	*
Vagina		*

§ Weighed after fixation
* Organs to be weighed and/or tissue samples to be fixed

APPROVED PROTOCOL

7.2 Reporting

Brief summaries will be submitted to the monitor at monthly intervals. Any unexpected findings during the course of the study will be reported immediately.

The final report will be in the format required for submission to the EPA/FIFRA regulatory authority.

An advance photocopy (draft) of the final report will be sent to the Sponsor. With the exception of the dated signature of all scientists and other professional staff, the draft will contain all the information and data included in the final report. Comments made by the Sponsor may be incorporated into the draft, after which it will be issued as the final report.

Four copies of the final report, one unbound and printed single sided, and one copy of any photographic reports will be issued to the Sponsor.

Any additions or corrections to the final report will be in the form of an amendment by the Study Director. The amendment, clearly identifying that part of the final report that has been added to or corrected and the reasons for the addition or correction, will be signed and dated by the person responsible.

7.3 Archives

The following data and specimens will be retained during the study and subsequently for at least five years. After this period the Sponsor will be contacted for approval before disposal of any data or specimens; no data or specimens will be destroyed without the consent of the Sponsor. Data and specimens will be retained in the archives for a further specified period at the Sponsor's request.

Protocol, Amendments to Protocol and Study Notes

Animal arrival
Tattoo records
Allocation to cages and dosage group
Battery plan

Diet receipt information
Analytical details of - diet : certificates from supplier and in-house work sheets and reports
water : in-house work sheets and reports

Information on the test substance - from Sponsor (e.g. identity, strength, quality, purity and stability)
Record of sample receipt
Formulation requests
Formulation details - weighing out of the test substance
Stored samples of the test substance

APPROVED PROTOCOL

Formulation Quality Control records
Formulation stability, homogeneity and achieved concentration assay requests, work sheets and reports (if performed)

Environmental details of animal rooms : temperature
relative humidity
air-changes
Outside temperature and humidity

Pre-treatment animal observations
Daily animal observation records, including any incidents that may have affected the quality or integrity of the study
Food consumption records
Water consumption records (if performed)
Bodyweight records

Necropsy requests and reports, including organ weights
Final macroscopic report
Tissues
Histology requests, blocks, slides, pathology assessment and final microscopic report (if examined)

Records of training and experience of all relevant personnel
Records of maintenance and calibration of equipment

Photographic films (if any)
Computer prints and permanent storage discs, including data edits
Correspondence

Reports - typescript and manuscript of draft and final versions

7.4 Quality assurance

Preliminary studies such as this are not routinely subjected to specific (study based) Quality Assurance inspections. However, procedures similar to those used on this type of study will be inspected periodically in the laboratory and animal areas.

The procedures and data for this study will be subjected to specific examination, and the final report reviewed by the Q.A. Unit, only if requested by the Sponsor.

All raw data pertaining to the study will be available for inspection by any person nominated by the Sponsor.

LSR Schedule No : RHA/422/46030
LSR Enquiry No : 4968A
Protocol Amendment No : 1
No. of pages : 3

M&B 46030: PRELIMINARY TOXICITY STUDY BY DIETARY ADMINISTRATION TO CD RATS FOR FOUR WEEKS

Study Director : P. Aughton, B.Sc., Dip.R.C.Path., C.Biol., M.I.Biol.

The signature of the Study Director authorises the implementation of this amendment to protocol from the effective date shown on page 2. Any changes to the study design after the date of this authorising signature will be documented in a further formal amendment.

FIRST AMENDMENT APPROVAL

For LIFE SCIENCE RESEARCH LIMITED

Issued by : P Aug..... (Study Director) Date: 16 August '90

Released by: ..... Date: 16 August 1990

For RHÔNE-POULENC AGROCHIMIE

Approved by: ..... Date: 20/8/90

LSR Schedule No : RHA/422/46030
Protocol Amendment No : 1

M&B 46030: PRELIMINARY TOXICITY STUDY BY DIETARY ADMINISTRATION TO CD RATS FOR FOUR WEEKS

Reasons for amendments : Section 4.4 : Dietary analyses not requested by the Sponsor therefore section deleted. Requirement for trial mix also deleted.

: Sections 6.2, 6.3 and 6.4 : Delection of requirement to weigh organs and to retain tissue samples at the request of the Sponsor (N. Carmichael's fax of 13.08.90).

Effective date : 13 August 1990

Amendments

4. Treatment

4.4 Quality control of dosage form

Section to read:

On each day that quantities of test substance are to be weighed out for test diet preparation, the stock container of test substance will be weighed before the first and after the last removal of part of its contents. The reduction in the weight of the stock container will be documented as a check that the required amount of the test substance has been used.

6. Terminal observations

6.2 Macroscopic pathology

Section to read:

All animals killed and any found dead will be subjected to a detailed necropsy.

The necropsy procedure will include a review of the history of each animal and a detailed examination of the external features and orifices, the neck and associated tissues and the cranial, thoracic, abdominal and pelvic cavities and their viscera. The external and cut surfaces of the organs and tissues will be examined as appropriate.

6.3 Organ weights

Section delected.

6.4 Tissues preserved in fixative

Section deleted.

Pathology Procedures Table deleted.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Glenn S. Simon, Ph.D., DABT
Director of Toxicology
Rhône-Poulenc
P.O. Box 12014
2 T.W. Alexander Drive
Research Triangle Park, North Carolina 27709

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MAR 0 6 1995

EPA acknowledges the receipt of information submitted by your organization under Section 8(e) of the Toxic Substances Control Act (TSCA). For your reference, copies of the first page(s) of your submission(s) are enclosed and display the TSCA §8(e) Document Control Number (e.g., 8EHQ-00-0000) assigned by EPA to your submission(s). Please cite the assigned 8(e) number when submitting follow-up or supplemental information and refer to the reverse side of this page for "EPA Information Requests".

All TSCA 8(e) submissions are placed in the public files unless confidentiality is claimed according to the procedures outlined in Part X of EPA's TSCA §8(e) policy statement (43 FR 11110, March 16, 1978). Confidential submissions received pursuant to the TSCA §8(e) Compliance Audit Program (CAP) should already contain information supporting confidentiality claims. This information is required and should be submitted if not done so previously. To substantiate claims, submit responses to the questions in the enclosure "Support Information for Confidentiality Claims". This same enclosure is used to support confidentiality claims for non-CAP submissions.

Please address any further correspondence with the Agency related to this TSCA 8(e) submission to:

Document Processing Center (7407)
Attn: TSCA Section 8(e) Coordinator
Office of Pollution Prevention and Toxics
U.S. Environmental Protection Agency
Washington, D.C. 20460-0001

EPA looks forward to continued cooperation with your organization in its ongoing efforts to evaluate and manage potential risks posed by chemicals to health and the environment.

Sincerely,

Terry R. O'Bryan

Terry R. O'Bryan
Risk Analysis Branch

Enclosure 12198A

Triage of 8(e) Submissions

Date sent to triage: APR 06 1995

NON-CAP (CAP)

Submission number: 12198A

TSCA Inventory: Y N (D)

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX (SBTOX) SEN (w/NEUR)

Group 3 - Elizabeth Margosches (1 copy each)

STOX	CTOX	EPI	RTOX	GTOX
STOX/ONCO	CTOX/ONCO	IMMUNO	CYTO	NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

For Contractor Use Only

entire document: (0) 1 2 **pages** 1,2 **pages** 1,2, tabs

Notes: 2-sided

Contractor reviewer : LPS **Date:** 12/22/94

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ- 1192 - 12198 SEQ. A

TYPE: (INT) SUPP FLWP

SUBMITTER NAME: Rhone - Poulenc Inc.

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0639) REFER TO CHEMICAL SCREENING
(0678) CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKERS/OTHERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP./USE DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB. DATE: 10/27/92 OTS DATE: 11/02/92 CSRAD DATE: 08/12/94

CHEMICAL NAME:
1H-pyrazole-3-carbonitrile, 5-amino-1-[2,6-dichloro-4-(trifluoromethyl)phenyl]-4-[(trifluoromethyl)sulfinyl]-

CAS#
120068-37-3 → m+B 46030

INFORMATION TYPE:		P F C	INFORMATION TYPE:		P F C	INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04	0216	EPI/CLIN	01 02 04	0241	IMMUNO (ANIMAL)	01 02 04
0202	ONCO (ANIMAL)	01 02 04	0217	HUMAN EXPOS (PROD CONTAM)	01 02 04	0242	IMMUNO (HUMAN)	01 02 04
0203	CELL TRANS (IN VITRO)	01 02 04	0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04	(0243)	CHEM/PHYS PROP	01 02 04
0204	MUTA (IN VITRO)	01 02 04	0219	HUMAN EXPOS (MONITORING)	01 02 04	0244	CLASTO (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04	0220	ECO/AQUA TOX	01 02 04	0245	CLASTO (ANIMAL)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04	0221	ENV. OCCC/REL/FATE	01 02 04	0246	CLASTO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04	0222	EMER INCI OF ENV CONTAM	01 02 04	0247	DNA DAM/REPAIR	01 02 04
0208	NEURO (HUMAN)	01 02 04	0223	RESPONSE REQEST DELAY	01 02 04	(0248)	PROD/USE/PROC	01 02 04
(0209)	NEURO (ANIMAL)	01 (02) 04	0224	PROD/COMP/CHEM ID	01 02 04	0251	MSDS	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04	0225	REPORTING RATIONALE	01 02 04	0299	OTHER	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04	0226	CONFIDENTIAL	01 02 04			
0212	ACUTE TOX. (ANIMAL)	01 02 04	0227	ALLERG (HUMAN)	01 02 04			
(0213)	SUB ACUTE TOX (ANIMAL)	01 (02) 04	0228	ALLERG (ANIMAL)	01 02 04			
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04	0239	METAB/PHARMACO (ANIMAL)	01 02 04			
0215	CHRONIC TOX (ANIMAL)	01 02 04	0240	METAB/PHARMACO (HUMAN)	01 02 04			

TRIAGE DATA:	NON-CBI INVENTORY	ONGOING REVIEW	SPECIES	TOXICOLOGICAL CONCERN:	USE:	PRODUCTION:
	YES	YES (DROP/REFER)	RAT	LOW	R&D pesticide	
CAS SR	NO	NO (CONTINUE)		MED		
	(DETERMINE)	REFER:		(HIGH)		

COMMENTS: 8eha-0191-11625, 0391-11995, 0591-12325, 0791-12845, 0791-12855, 0891-13155, 0392-25405

-CPSS-

> <ID NUMBER>
8(E)-12198A

> <TOX CONCERN

H

> <COMMENT>
SUBCHRONIC ORAL TOXICITY IN MALE AND FEMALE CD RATS IS OF HIGH CONCERN. DOSES OF TEST MATERIAL SUPPLIED IN THE DIET TO 4 GROUPS OF 5 MALE AND 5 FEMALE RATS WERE ASSOCIATED WITH SIGNS OF NEUROTOXICITY AND DEATH. GROUPS RECEIVED EITHER 500 (25 MG/KG), 750 (37.5 MG/KG), 1000 (50 MG/KG) OR 1500 PPM (75 MG/KG) IN THE FEED. ANIMALS AT THE TWO HIGHEST DOSAGES EITHER DIED OR WERE SACRIFICED IN THE FIRST FEW DAYS OF TREATMENT, BUT MORTALITIES WERE NOTED AT ALL TREATMENT LEVELS. OVERT SIGNS OF NEUROTOXICITY WERE OBSERVED IN DECEDENTS INCLUDING PILOERECTION, HUNCHED POSTURE AND SPASTIC MUSCLE REACTION. BODYWEIGHT AND FOOD CONSUMPTION WERE DEPRESSED IN ALL RATS RECEIVING 37.5 MG/KG OR MORE PER DAY. PATHOLOGICAL SIGNS OF TOXICITY INCLUDED STOMACH DISTENTION WITH ABNORMAL CONTENTS, FACIAL AND PERINEAL STAINING AND DARK LUNGS.

$$$$